Cleveland Clinic Quarterly

Volume 23
1956

Cleveland, Ohio

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UROLOGIC CAUSES OF HYPERTENSION

I. Hypertension Due to Renal Artery Lesions

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CONCEPTS OF HYPERTENSION have undergone significant changes during the past fifty years. The early concept that hypertension was the result of a defective arterial circulation and that to lower blood pressure would be detrimental to life was slowly replaced by a recognition that high blood pressure plays an important role in the maintenance and/or progression of hypertensive vascular disease. Much of the advance in the understanding of clinical hypertension is based upon studies of experimental hypertension. Twenty years ago, hypertension was first produced in animals by (1) section of the sino-aortic depressor nerves (Koch and Mies), (2) constriction of the renal artery (Goldblatt), and (3) production of perinephritis (Page). Subsequently, experimental endocrine hypertension was elicited in rats (Selye) and the hypertension of coarctation of the aorta experimentally reproduced in dogs, although participation of renal mechanisms in the latter has not yet been fully defined.

Hypertension is now looked upon as but one manifestation of a systemic disease. Clinically, the course varies from a relatively benign state, in which the only abnormality is elevated blood pressure to a fulminant process, with widespread arteriolar necrosis. Two broad etiologic categories of hypertensive diseaes are recognized. These are: (1) *primary* or *essential* hypertension, for which no single cause is demonstrable; it probably has a genetic basis and includes conditions, such as the hypertensive diencephalic syndrome, which may have specific etiologies; (2) the *secondary* hypertensions; these have recognizable causes, although the pressor mechanisms may not yet be fully understood.

In most patients, the diagnosis of *primary* or *essential* hypertension is made by exclusion. It should be emphasized that hypertension of recent onset in a person less than 35 years of age who does not have a family history of hypertensive disease, as also the sudden onset of severe or malignant hypertension in an older person, should be considered secondary until thorough study has excluded definable causal mechanisms.

The mechanisms of the secondary hypertensions may be grouped as (1) renal, (2) endocrine, (3) cardiovascular, and (4) neurogenic.[1] Renal hypertension is associated with lesions of the renal artery or with parenchymal disease.

Endocrine hypertension is seen in Cushing's syndrome, primary aldosteronism, and pheochromocytoma. The common types of cardiovascular hypertension occur with coarctation of the aorta and with aortic arteriosclerosis. The hypertensions associated with bulbar neuropathy in poliomyelitis and acute porphyria are neurogenic.

Clinical and experimental renal hypertensions are thought to be humorally mediated through the renal pressor system. Initially, some change in the renal circulation causes release of an excessive amount of the enzyme, renin; this acts on circulating renin-substrate to split off angiotonin; the latter is a pressor and vasoconstrictor polypeptide that elicits hemodynamic changes comparable to those that characterize hypertension and, experimentally, can elicit lesions of hypertensive disease.[2] The workings of the renal pressor system have not been well enough defined to accept it as the sole etiologic factor in renal hypertension. Recent studies indicate that secondary mechanisms may participate in the persistence of hypertension. These are adrenal,[3] neural,[4] and other renal factors.[5]

The purpose of this report is to review some of the clinical characteristics, diagnostic procedures and pathologic findings in one form of renal hypertension —that associated with lesions of the renal arteries. It is important that this condition be recognized, for it usually is remediable, often occurs in young people, and frequently assumes a rapidly destructive course.

RENAL ARTERY LESIONS

Historical Background

There are comparatively few well-documented reports of hypertension due to renal artery lesions. In a recent review of nonembolic renal artery occlusion as a cause of renal hypertension,[6] there were listed 21 autopsy reports and 15 case reports of patients who had been relieved of hypertension by nephrectomy or thromboendarterectomy; three additional case reports of occlusive renal artery disease with hypertension were presented. Pastor and associates[7] have since reported a case of hypertension, relieved by nephrectomy, associated with a ruptured renal artery aneurysm. A recent Cabot Case[8] described a patient who died of a dissecting thoracic aneurysm who also had had progressive hypertensive vascular disease associated with partial occlusion of a renal artery. A number of patients with embolism of the renal artery have been reported who had transient or persistent hypertension depending on the degree of renal infarction resulting from the sudden blocking of the artery.[9,10]

Pathology

Obstructive renal artery lesions can be divided into two main groups: *extrinsic compression* and *intrinsic arterial disease*. Both are capable of causing renal hemodynamic changes and possibly of initiating the release of renal pressor

substances. Extrinsic causes of compression of the renal artery, such as aortic aneurysm or retroperitoneal tumor, are rare, and will not be discussed here. The intrinsic types of renal artery disease include *embolism*, *thrombosis*, *developmental defects associated with fibrous intimal proliferation*, *aneurysm*, *arteriosclerotic plaques*, and *syphilitic arteritis*.

An *embolus*, almost invariably from a diseased heart, may obstruct the renal artery or one of its branches and thereby cause partial or total infarction of the kidney. Total necrosis of the kidney does not cause hypertension,[11] but partial infarction of the kidney and reduced blood supply in other areas may cause transient reversible hypertension or severe persistent hypertension.[9,10] Laforet[12] reported the cases of three young men who died of malignant hypertension associated with renal artery lesions, one of which was a metallic embolus of the renal artery. The embolus was a shell fragment that originally had lodged in the chest but later entered the blood stream and occluded the left renal artery. Progressive malignant hypertension resulted, and the patient died shortly thereafter.

Thrombosis of the renal artery or one of its branches may produce hypertension. When there is only one artery supplying blood to the kidney, thrombosis

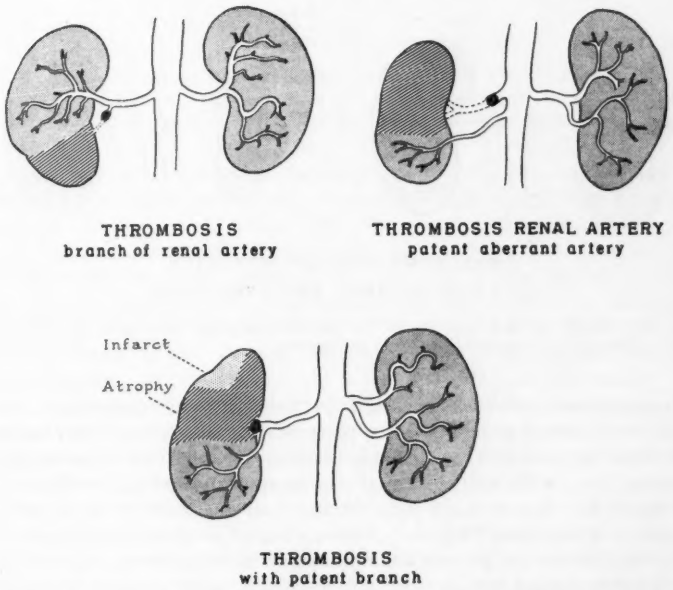
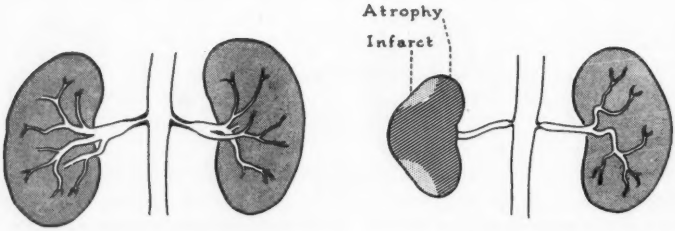


Fig. 1. Renal artery thrombosis associated with hypertension, showing variation in blood supply and renal damage. Embolism may simulate thrombosis. (Adapted from renal angiograms.)

of that artery will cause total infarction without producing hypertension.[13] If one or more patent aberrant arteries exist, or if only a branch of the renal artery is thrombosed, a portion of the kidney will remain viable, but part of the kidney will have reduced blood supply and hypertension commonly ensues. We have observed and treated four patients with thrombosis of the renal artery associated with severe hypertensive vascular disease. The variations in blood supply, sites of thromboses, and degrees of renal infarction or atrophy are illustrated in Figure 1.

Hypertension in young people sometimes results from what may be considered *developmental defects* of the renal artery. In our experience these defects are bilateral and consist of stenosis of the aortic orifices of the renal arteries, or narrowed segments of the vessels (Fig. 2). In each patient, the bilateral lesions are similar from the roentgenographic and pathologic standpoints. In addition to reduction in diameter of the vessel itself, *fibrous proliferation of the intima* occurs in the narrowed portions and constricts the lumen still more. The result is inadequate renal circulation, release of circulating renal pressor substances and progressive hypertension. We have seen three patients, one reported elsewhere,[14] who developed severe hypertensive vascular disease shortly after puberty or in young adulthood as a result of this type of lesion.



DEVELOPMENTAL DEFECTS WITH
FIBROUS INTIMAL PROLIFERATION

Fig. 2. The shaded areas within the narrow portions of the renal arteries indicate fibrous intimal proliferation. (Adapted from renal angiograms.)

Hypertension has been reported in patients with congenital saccular *aneurysm* of the renal artery.[7,15] Most patients with aneurysm of the renal artery do not have hypertension, presumably because the aneurysm does not interfere with blood flow to the kidney. Renal angiography showed no interference with renal blood flow in our seven patients who had aneurysm of the renal artery or of one of its branches. Only one of these seven patients has been hypertensive, but in this instance the patient also has an arterial lesion of the opposite kidney (Fig. 3, upper right-hand corner). This patient is under medical antihypertensive treatment at the present time.

The formation of hard *arteriosclerotic plaques* at the aortic orifices or within the renal artery constricts the lumen and interferes with blood flow. These

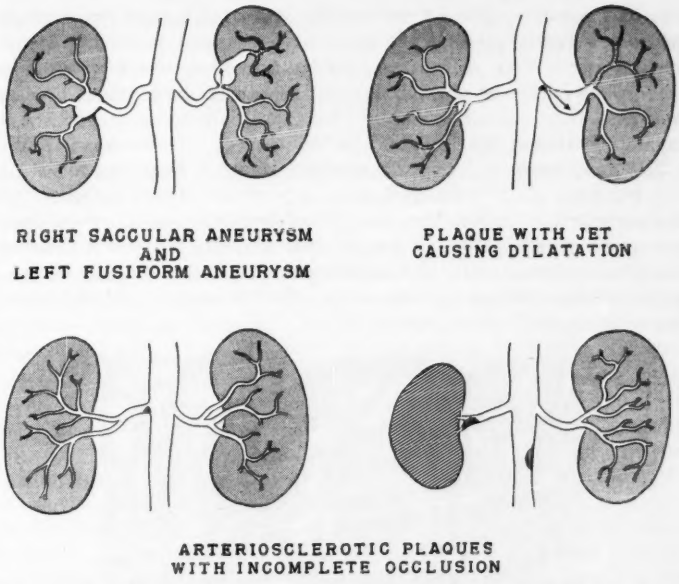


Fig. 3. Variations of hard arteriosclerotic plaques of the renal artery associated with hypertension. The jet dilatation of fusiform aneurysm effect is diagrammed. Congenital saccular aneurysms occasionally are associated with hypertension. (Adapted from renal angiograms.)

plaques usually are a local manifestation of generalized arteriosclerosis. We have had eight patients with severe hypertensive vascular disease who were shown by aortography to have arterial filling defects characteristic of this type of lesion (Fig. 3). Fusiform dilatation of the artery distal to the occluding plaque was demonstrated in three of these eight patients. It is believed that this dilatation of the artery results from the deflection of the blood stream by the obstructing plaque against the arterial wall, and that it is similar to the jet-action aneurysm occurring just beyond the coarctate segment of thoracic aorta. Dilated segments of arteries are abnormal and may be structurally weak. Rupture of the dilated aneurysmal renal artery and severe hemorrhage occurred in one patient; but since the lesion already had been recognized, nephrectomy was immediately performed. This patient recovered and has had a three-year remission of malignant hypertension.

A few instances of *syphilitic arteritis* with incomplete occlusion of the renal arteries associated with malignant hypertension have been reported.[16]

Laforet[12] has presented an excellent description of the pathologic changes found in both kidneys of three patients who died of malignant hypertension as the result of unilateral renal artery obstruction. In each case, the kidney with impaired blood supply showed tubular atrophy, a relative increase in interstitial tissue, and benign nephrosclerosis. The opposite kidney with the intact

renal artery, however, showed necrotizing arteriolar lesions characteristic of malignant nephrosclerosis. The situation is very similar to that described by Wilson and Byrom[17] in rats with renal hypertension, where nephrosclerotic changes developed in the normal kidney, but not in the kidney whose artery was compressed.

Any constriction of the lumen of the renal artery with impairment of renal blood flow may cause reduction in the size of the kidney and focal tubular atrophy, but most of the renal epithelium is preserved. There are no significant changes in the arterioles. Further reduction of the blood flow into the kidney will result in more atrophy (Fig. 4) and possibly zones of infarction. Two of our patients with reversible malignant hypertension due to renal artery disease, had no significant reduction in the size of the affected kidneys and the pathologic changes were correspondingly minimal.

Fig. 4. Photomicrograph of lower pole of the kidney (also see Figure 9) showing the line of demarcation between the normal renal parenchyma above and the zone of atrophy below, resulting from diminished blood supply. X110.

Diagnosis of Renal Artery Lesions

Hypertension should be considered a diagnostic problem, especially in the young adult, in the elderly person, or in those patients in whom there is no

family history of essential hypertension. The *sudden onset of hypertensive vascular disease following an attack of flank pain* should make one consider the possibility of thrombosis or of embolism of a renal artery.[18] The history of a patient with thrombosis of the renal artery is diagrammatically presented in Figure 5. Of more insidious onset is the hypertensive vascular disease caused by partial or incomplete obstruction of the renal artery, usually due to arteriosclerotic plaques (Fig. 6). These plaques may develop at any age, but are more likely to occur in elderly people.

Intravenous urography for visualization of the upper urinary tract should be performed in all nonazotemic hypertensive patients. There are no pathologic changes in the renal pelvis or calyces, except possibly reduction in size, in patients having lesions obstructing the renal artery; but there may be significant decreases in excretory function. Thrombosis of the renal artery will produce a nonfunctioning kidney; but if a patent aberrant artery is present, *the intravenous urogram may reveal essentially normal excretory function with only slight reduction in renal mass and may be regarded as normal* (Fig. 7). When occlusion of a renal artery is incomplete, the appearance-time of the injected contrast medium may be slightly delayed in the kidney with impaired blood supply, and the concentration of medium in the pelvis and calyces may be diminished. However, these changes can be minimal despite serious obstructive lesions of the renal artery.

In the recognition of impaired renal function due to renal artery lesions, an important aid is the comparison of urine samples obtained from both kidneys by ureteral catheterization. Severely ischemic kidneys may be anuric or oliguric. The appearance-time of injected dyes, such as indigo carmine, is delayed. Where the circulatory defect is less severe, the excretory functions of both kidneys may be compared by determinations of urinary osmolarity and electrolyte concentrations and concentrations of injected para-aminohippuric acid (PAH) in the separate urine samples. An example of the findings by this procedure is shown in the Table. The patient, a 33-year-old man, had malignant hypertension. The

Table.—*Comparison of excretory functions of the kidneys in patient with malignant hypertension*

Condition of kidneys	Osmolarity (mOsm./l.)	PAH (mg.%)	Na (mEq./l.)	K (mEq./l.)
Normal	418	790	12	26
With constricted artery	362	514	9	24

intravenous urogram in this patient was considered to be normal at first examination; aortography showed partial constriction of the left renal artery with jet dilatation (Fig. 3, upper right-hand corner), and review of the urogram showed some decrease in size of the left kidney.

Translumbar aortography is the only means of demonstrating the presence of renal artery defects. It should be utilized in all patients with hypertension in whom such lesions are suspected. The procedure for aortography has been previously described.[19] To obtain the utmost cooperation from the patient and to minimize the hazards of translumbar aortography, local anesthesia is used

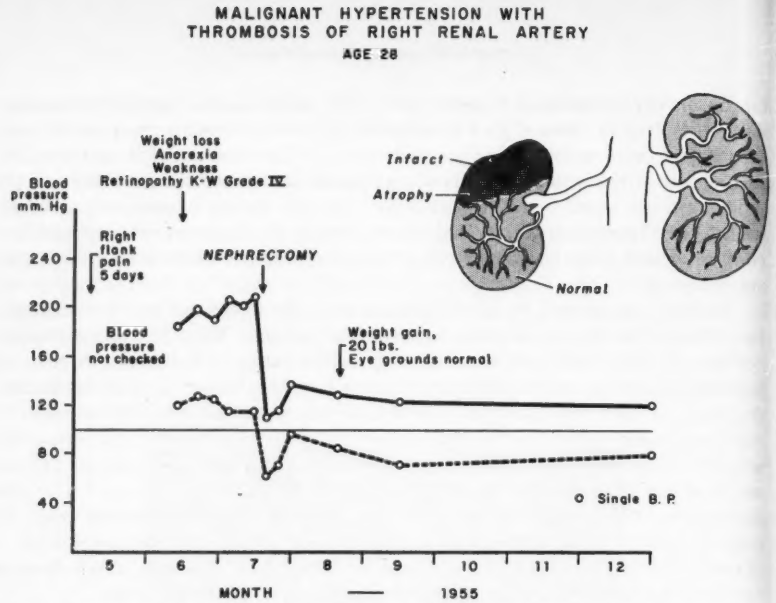


Fig. 5. Diagram of clinical course of acute onset of malignant hypertension in a young man who had had what was considered to be pyelonephritis. The preoperative aortogram showed complete occlusion of the main artery as indicated in the diagram. (Also see Figure 7.) Six months after nephrectomy he was completely well.

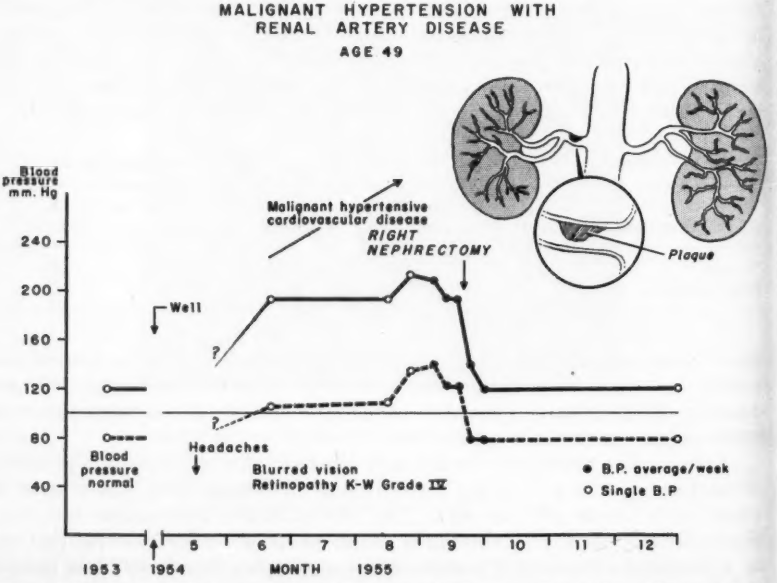


Fig. 6. Diagram of clinical course of rapidly progressive hypertension without history of flank pain. The defect in the right renal artery disclosed by preoperative aortography is diagrammed. The kidney was normal in size and showed only focal tubular atrophy. Three months after nephrectomy the patient was completely well.

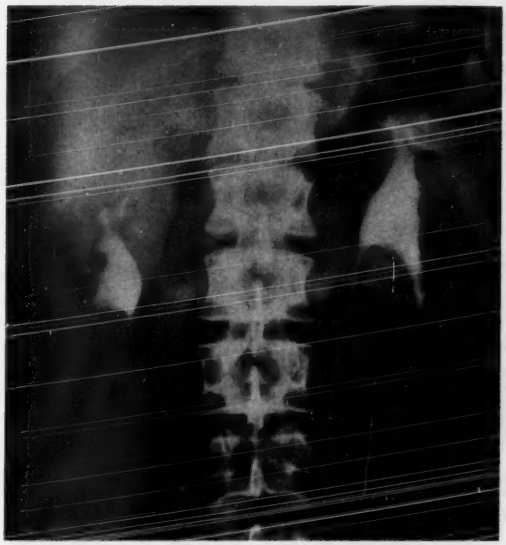


Fig. 7. Intravenous urogram of patient (also see Figure 5) who had thrombosis of the right main renal artery with a patent branch. There is slight reduction in the size of the right kidney; excretory function appears to be normal.

during the examination. In patients with extremely elevated blood pressure it is helpful to use vasodepressor drugs, such as sodium nitroprusside, hydralazine, (Apresoline*) or trimethaphan camphor sulfonate (Arfonad**), to reduce the blood pressure and thereby obtain better compression of the aorta distal to the renal arteries and filling of the arteries themselves.[20] The aortogram may demonstrate a filling defect in the renal artery, a narrowed lumen, absence of an important branch, reduction in the vascular system of the affected kidney, or delay in filling of the arterial system past the obstructing lesion (Figs. 8 and 9).

Results of Treatment

In patients with acute malignant hypertension of brief duration caused by a lesion obstructing a renal artery, nephrectomy results in a prompt fall in blood pressure to normal and reversal of hypertensive vascular disease. In patients with hypertension that has progressed gradually to hypertensive vascular disease, the fall in blood pressure is more gradual, reaching normal levels in two or more weeks postoperatively. The secondary mechanisms of renal hypertension, noted above, probably contribute to the persistence of the hypertensive state after nephrectomy in these latter cases.

**Apresoline, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.*
***Arfonad, Hoffman-La Roche, Inc., Nutley, New Jersey.*

Fig. 8. Aortogram demonstrating narrow developmental defects of both renal arteries in a 15-year-old boy with hypertension (also see Figure 2). Note the distal dilatations of the left renal artery. Such a lesion is amenable only to replacement arterial surgery.

Fig. 9. Translumbar aortogram shows absence of branch of main renal artery to lower pole of right kidney (also see Figure 4). This blood vessel was approximately 70 per cent occluded by fibrous tissue. The patient was 28 years of age and had onset of moderately severe hypertension four months after an attack of renal colic. He was relieved of hypertension by nephrectomy.

In three of our four patients with renal artery thrombosis and acute hypertension, nephrectomy was followed by immediate and permanent reversal of the hypertensive state.[6] For several days following nephrectomy, one of the three patients had hypotension and oliguria, presumably resulting from the rapid change in the blood pressure. The blood pressure in the fourth patient gradually returned to normal over a period of several months postoperatively. These patients were all men, ranging in age from 28 to 52 years.

Among the eight patients with hypertension associated with obstructive arteriosclerotic plaques of the renal artery, generalized vascular disease was so advanced in two that surgery was contraindicated; both patients now are dead. A third patient is under medical treatment at this time. Of the remaining five patients, two men, 33 and 49 years of age, respectively, had prompt remission of the syndrome of malignant hypertension following nephrectomy. The results of nephrectomy in the remaining three patients, although less dramatic, are of considerable interest. All three were elderly patients who were known to have had mild or moderate arteriosclerotic hypertension for at least several years prior to the sudden onset of malignant hypertension. In each patient, after nephrectomy, the blood pressure returned to the level that had been observed before the malignant phase of hypertension supervened. Of the latter three patients, one underwent nephrectomy three years ago and has had reversal of progressive hypertensive vascular disease; the hypertensive states in the other two are in remission, but treatment is too recent to allow final evaluation.

Two of the three young patients with bilateral developmental defects of the renal artery died in the hospital. The third has recently undergone surgical correction of both defects by means of freeze-dried artery homografts between the aorta and the distal, normal, renal artery.[21] A gradual fall in blood pressure to normal over a two-week period followed the second renal artery homograft. No alteration of renal excretory function occurred postoperatively.

During operation, a pronounced thrill frequently has been palpable in the partially occluded renal artery. In one patient an effort was made to determine the intra-arterial pressure distal to the occlusion but the pressure was insufficient to produce a reliable reading. In another patient, an immediate fall in peripheral blood pressure of 50 mm. Hg occurred when the partially occluded renal artery was manually compressed. When the vessel was released, the blood pressure promptly rose to former levels. This phenomenon was repeated several times. When the normal renal artery to the opposite kidney was manually compressed, no change in blood pressure was noted.

It also has been noted that the kidney with impaired circulation is soft and flabby compared with the opposite kidney with normal circulation. Both kidneys in the patient who had homografts of defective, narrowed renal arteries became tense as soon as circulation was established through the grafted arteries.

COMMENT

The role of the kidneys as an etiologic factor in hypertension has been under active study for two decades. Until recently, emphasis has been placed on

primary parenchymal renal disease, such as pyelonephritis, and on obstructive uropathy as the chief causes of secondary renal hypertension. When the disease was seemingly unilateral, nephrectomy frequently was performed in the hope of removing the cause of the hypertension. Results often were disappointing. These findings will be discussed in Part II of this paper in a forthcoming issue of this Journal.

Gradually more and more cases of unilateral renal artery lesions associated with *malignant, progressive hypertensive vascular disease* have been reported. This hypertension closely simulates experimental hypertension elicited by partial compression of a renal artery. The results of nephrectomy for this type of lesion are dramatically good—a prompt or gradual fall in blood pressure, depending on the duration of antecedent hypertension, with remission of hypertensive vascular disease.

The history and the findings on examination of each hypertensive patient must be carefully evaluated before the condition is accepted as primary or essential. On the basis of this evaluation, the experienced physician can select those patients who may have secondary renal hypertension and recommend their further study by procedures outlined above.

The chief pitfalls in the diagnosis of renal artery lesions as a cause of hypertension, are the misinterpretation of inadequate aortograms and the failure to appreciate the significance of even minor variations from normal in the comparative sizes of the kidneys or their excretory functions, as shown by intravenous urography. The comparison of excretory functions of both kidneys is a valuable adjunctive measure in the diagnosis of renal hypertension. Aortography provides the only accurate means of demonstrating renal artery lesions, and should be more widely used when secondary renal hypertension is suspected. There are recognized hazards to translumbar aortography but, in selected cases, the risk involved is far outweighed by the possible benefit which will accrue from the discovery and relief of the cause of the hypertensive state.

Summary

Renal artery lesions that may produce hypertensive disease are embolism, thrombosis, developmental defects associated with fibrous intimal proliferation, aneurysm, arteriosclerotic plaques, and syphilitic arteritis. These lesions interfere with blood flow through the renal artery; they may go on to reduce the blood supply to part or all of the kidney, so that zones of renal atrophy or infarction may result. At some point in this process renal pressor substances are released that initiate vasoconstriction and hypertension.

Diagnosis of renal artery lesions as a cause of hypertension is made by careful evaluation of intravenous urograms, comparison of excretory functionings of both kidneys, and demonstration of the defect by aortography. A history of the sudden onset of nonfamilial hypertension, particularly after an attack of flank pain, is suggestive of the presence of this condition.

In properly selected patients, removal of the kidney having impaired blood supply will reverse the hypertensive state. A patient with bilateral renal artery stenosis of developmental origin has recently undergone successful homografting of both renal arteries.

Acknowledgment

We wish to thank William J. Engel, M.D., Department of Urology; and Fay A. LeFevre, M.D., and William L. Proudfit, M.D., Department of Cardiovascular Disease, for the referral of some of the patients described in this study.

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SURGERY FOR METASTATIC NEOPLASTIC DISEASE IN THE LUNG

Review of 38 Cases

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METASTATIC neoplastic disease in the lung ordinarily is not a surgical problem. The consideration of surgery arises only under exceptional circumstances. The lungs are a common site of metastatic neoplasms. This frequency is readily explainable on anatomic and physiologic bases. Roentgenography offers unique ability to screen the lungs for disease of many types, and has certainly served to emphasize the frequency of pulmonary metastatic neoplastic disease. The routine use of roentgenograms of the chest in the follow-up of patients having cancer reveals a significant number of metastases, and also the great increase in the use of periodic survey films brings to light a large group of pulmonary neoplasms, a number of which turn out to be metastatic from latent primary tumors. Also a diffuse pulmonary lesion may on occasion prove to represent atypical neoplastic disease.

We have performed thoracotomies on a number of patients having metastatic disease in the lung. In an effort to define the surgical indications and to evaluate the results, we have reviewed the findings in 38 cases in which neoplastic tissue considered to be metastatic in origin (Table 1) was obtained. A number of additional cases have been excluded in which histopathologic findings were indeterminate as to primary source of the lesion, and the clinical picture was consistent with primary bronchogenic neoplasm. A review of these 38 cases has permitted the definition of the broad surgical indications discussed below, and we believe that the results justify the continued use of surgical treatment in carefully selected patients.

Indications for Surgery

The indications for surgery in these patients can be broadly grouped as follows:

1. *Diffuse or multicentric disease (biopsy as a planned minimal procedure for diagnosis or confirmation of suspected diagnosis).*
2. *Solitary, circumscribed, "coin" lesion.*
3. *Suspected solitary neoplastic metastasis.*
4. *Presumed primary pulmonary neoplasm.*
5. *Metastatic neoplastic lesions obstructing a bronchus (operation, usually clearly for palliation only).*

Table 1. — *Analysis of 38 cases of metastatic neoplastic disease in the lung*

Table 1.—Analysis of 38 cases of metastatic neoplastic disease in the lung

Operative procedure	No. of cases	Indications for surgery, no. of cases				
		Diffuse or multicentric disease	Solitary, circumscribed, "coin" lesion	Suspected solitary metastasis	Presumed primary neoplasm	Metastatic obstruction of bronchus
Lung biopsy as a planned minimal procedure	9	9	—	—	—	—
Exploratory thoracotomy with biopsy	11	—	—	2	9	—
Lobectomy or lesser resection	11	—	2	7	—	2
Pneumonectomy	7	—	—	4	1	2
TOTAL	38	9	2	13	10	4

All of the cases in this series can be classified in one of the above categories. There are, however, two additional situations which are worthy of mention in a discussion of this general subject: (1) a patient may have two separate primary carcinomas, and a history of malignancy elsewhere does not preclude the development of a primary bronchogenic carcinoma; (2) a pulmonary neoplastic lesion may be primary and the lesion elsewhere metastatic, a situation most frequently encountered at craniotomy.

The operative procedures performed in our 38 patients may be grouped as follows:

1. *Lung biopsy as a planned minimal procedure—9 patients*
2. *Exploratory thoracotomy with biopsy—11 patients*
3. *Lobectomy or lesser resection—11 patients*
4. *Pneumonectomy—7 patients*

ANALYSIS OF CASES

Diffuse or Multicentric Disease

Nine patients in our series underwent lung biopsy. Our procedure for biopsy is to make a small anterior intercostal thoracotomy, after local anesthesia with endotracheal intubation and mild general analgesia. For the past several years we frequently have employed this procedure for diagnostic purposes. Of the nine patients, five had had treatment for previous malignancy at a site other than the lungs, and biopsy was performed for definitive diagnosis because the clinical and roentgen findings were indeterminate. Two of the five patients had had removal of a carcinoma of the breast five and seven years, respectively, before lung biopsy; one patient had had an abdominoperineal resection for carcinoma of the rectum five years before; one had had irradiation therapy for carcinoma of the cervix one year before; and one had had an adenocystic salivary tumor removed 11 years before lung biopsy (Fig. 1).

Two other patients of the nine had multiple bilateral nodular densities throughout both lung fields, but in each the primary source of the metastasis was obscure. In each instance, histoplasmosis had been considered as a possible diagnosis. Biopsy in one of these patients, a 27-year-old man, showed an undifferentiated malignant neoplasm consistent with alveolar soft-part sarcoma[1] (Fig. 2). The other patient had an adenocarcinoma; the primary source of which never was found; postmortem examination was not performed.

The remaining two patients probably had primary bronchogenic adenocarcinoma with hematogenous metastases throughout both lung fields. However, the preoperative roentgenograms in one of these patients revealed a diffuse parenchymal infiltration that was believed to represent a pneumoconiosis (silicosis) (Fig. 3).

Lung biopsy had no significant therapeutic value for these patients (with the possible exception of one who had metastatic carcinoma of the breast, whose

(a)

(b)

Fig. 1. Roentgenograms obtained in 1951 (a) and in 1955 (b). (The patient had had an adenocystic parotid tumor removed in 1940). In 1951 a lung biopsy confirmed that the pulmonary nodules were histopathologically identical to the original tumor. The patient has no symptoms in the chest, but has pain from local recurrence at the primary site.

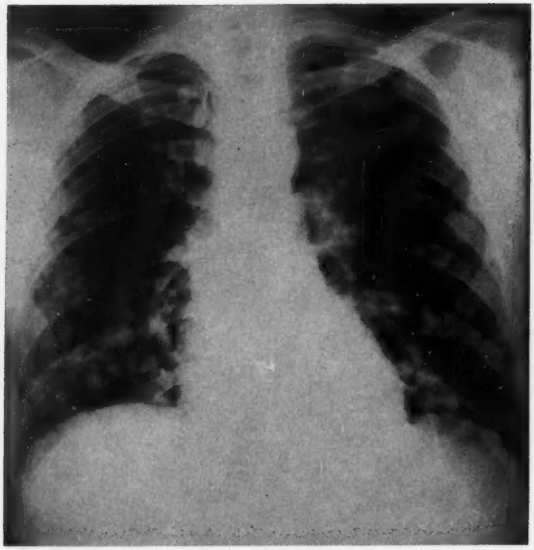

Fig. 2. Roentgenogram in a completely asymptomatic 27-year-old man. Diagnostic lung biopsy showed an alveolar soft-part sarcoma, and the patient subsequently died of disseminated neoplasm.

condition briefly improved on hormonal therapy); however, we believe that this minimal operative procedure had great diagnostic and prognostic value. In several instances, the histopathologic findings were a distinct surprise.

Solitary, Circumscribed, "Coin" Lesions

Approximately 50 per cent of coin lesions are found to be malignant when no calcium is apparent on roentgenograms.[2] Some of these malignancies are metastatic. The problem of an asymptomatic solitary lesion of the chest is being thought of more and more in terms of an aggressive surgical approach. Most of the patients who had circumscribed lesions in this series had a recent history of extrapulmonary malignancy, and are grouped in the category of *Suspected Solitary Metastasis*. However, in two patients the history of malignancy was not elicited until after removal of the pulmonary metastasis; these two cases are examples of the so-called *coin* lesion.

One of these patients, a 68-year-old woman, was found to have an oval mass, 4 cm. in diameter, in the left upper lobe, on roentgenograms taken because of recent minor hemoptysis. Papillary adenocarcinoma was found in the resected lobe. Ten years previously the patient had undergone hysterectomy, and on further investigation it was learned that a carcinoma, probably of ovarian

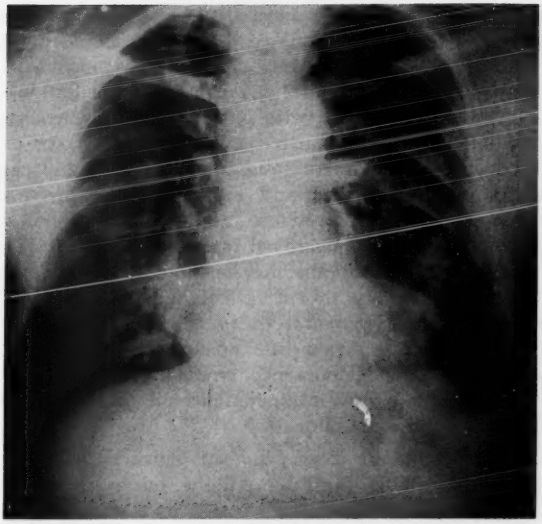

Fig. 3. Preoperative roentgenogram showing diffuse parenchymal infiltration believed to represent silicosis. The histopathologic findings were adenocarcinoma, probably of bronchogenic origin with hematogenous metastasis.

origin, had been removed at that time. The histopathologic material of both operations was subsequently compared and found to be identical. The patient is well two and one-half years following lobectomy.

The other patient underwent removal of a large solitary nodule from the left lower lobe. On histopathologic examination, the nodule proved to be a hemangiopericytoma. On reviewing the history and histopathologic material previously obtained, it was found that 13 years before thoracotomy a lesion of identical nature had been removed from the skin of the patient's back. Two years after thoracotomy, 15 years after the initial operation, a much smaller nodule was removed from the right lung, that also was identical to the original skin lesion.

Suspected Solitary Metastasis

In 13 of the 38 patients who underwent thoracotomy, the chief surgical indication was hope for cure of suspected solitary metastasis. Four of the 13 patients underwent pneumonectomy, seven lobectomy or lesser resections, and two only an exploratory thoracotomy with biopsy. Ten of the 13 patients had apparently solitary lesions, 1 had two lesions in the same lobe, and 2 each had a solitary lesion on each side. The two who underwent only exploration with biopsy were found at the time of surgery to have multiple, very small lesions, in addition to the larger readily apparent ones.

We believe that the minimal resection that allows total removal of a

metastatic lesion with a margin of normal tissue on all sides generally is indicated. However, in 4 of the 13 patients pneumonectomy proved necessary because of technical or anatomic considerations. One of the four patients was an operative mortality; he died after a right pneumonectomy had been performed for two oval lesions in the right upper lobe, which had appeared two years after a laryngectomy for carcinoma of the hypopharynx. Hilar nodes of the resected specimen at pneumonectomy were involved with metastatic cancer, and at postmortem examination adrenal and renal metastases were found. Two patients underwent pneumonectomy four, and five and one-half years, respectively, after combined abdominoperineal resections for rectal carcinoma. One of the two patients died ten months after pneumonectomy, of cerebral metastases; the other was well two years after pneumonectomy but subsequently was lost to follow-up. The fourth patient in the pneumonectomy group was operated upon three years after hysterectomy for adenocarcinoma. She died of spinal metastases nine months after pneumonectomy. Thus, in this small group, three of the four patients who underwent pneumonectomy were known to have had residual carcinoma at the time of death.

A more optimistic picture is seen in those seven patients who underwent lobectomy or lesser resections. Six still are living, but in three of these the postoperative follow-up has been less than a year. The one patient who died was a 24-year-old man who had a very large solitary lesion in the left lower lobe and a smaller one in the right middle lobe. Search for a primary source of the lesion was unavailing. A left lower lobectomy was performed for both diagnosis and treatment. During surgery, findings on frozen section established the diagnosis as embryonal carcinoma consistent with testicular origin; an extremely small, essentially nonpalpable, primary tumor was found in the testes and removed by orchiectomy. Postoperative irradiation was ineffective in the treatment of the lesion in the right lung; and six months after the first operation, middle lobectomy was performed. The patient died one year after the initial thoracotomy, with extensive pulmonary metastases.

One of the six living patients is well a year following wedge resection of a cylindromatous adenocarcinoma in the right lower lobe, which was metastatic from a parotid tumor first treated seven years before. She has also had resections of two cervical recurrences. In the second living patient, a small metastasis in the left upper lobe was resected approximately one year following amputation for hemangiopericytoma of the left femur. Fourteen months after resection, a second lesion in the right upper lobe appeared and was resected. The patient is well more than a year and one half following the second thoracotomy. The third living patient underwent right nephrectomy for a renal cell carcinoma in 1943. Seven years later, in 1950, he developed symptoms of an intracranial neoplasm, and a roentgenogram showed a lesion in the left lower lobe of the lung. He underwent craniotomy with resection of a cerebral metastasis and two weeks later a left lower lobectomy. This patient is well five and one-half years after the removal of the metastases. Two of the three patients who were recently treated, underwent resections of metastases from carcinoma of the breast; the third underwent resection of a metastasis of colonic origin.

The surgery performed on the remaining two patients who underwent exploration for what were presumably solitary metastases, represented rather heroic attempts to help young people. One was a 13-year-old girl who had a synovial sarcoma of the knee; the other was a 30-year-old woman who had chorio-epithelioma that apparently had been controlled in the abdomen.

Presumed Primary Neoplasm

In this group are included patients operated upon for definitive resection and a number of patients in whom the lesion if found to be neoplastic was certainly unresectable but in whom the diagnosis was obscure. One patient having a mass extending into the left hilum and negative bronchoscopic findings, underwent pneumonectomy for a neoplasm that on histopathologic study proved to be typical renal cell carcinoma. A right nephrectomy was performed shortly after pneumonectomy, but the patient died approximately six months after pneumonectomy of disseminated carcinoma in the retroperitoneal area. Nine additional patients underwent only exploration with biopsy for lesions that initially were believed to be primary carcinoma but that proved to be metastatic. In most of these cases the confusion concerning the diagnosis arose because the lesion caused segmental obstructive pneumonitis, a condition usually associated with bronchogenic neoplasms.

Metastatic Obstruction of a Bronchus

Ordinarily, metastatic lesions, in contrast to primary bronchogenic carcinoma, occur in the pulmonary parenchyma and do not involve the tracheobronchial tree. However, occasionally a metastatic lesion compresses or ruptures into a bronchus. If the compression or rupture is sudden, the patient may immediately develop respiratory symptoms similar to those seen in acute atelectasis. If the obstruction develops slowly, it causes obstructive pneumonitis and varying degrees of respiratory embarrassment. In rare instances resection of the obstructed portion of the lung may offer worthwhile palliation. For example, one of our patients had undergone left nephrectomy for renal cell carcinoma. When he was seen five years later, he had a one-year history of dyspnea, chronic cough with hemoptysis, and coughing up of small fragments of tissue. Roentgenograms of the chest showed multiple bilateral nodules, a collapsing left upper lobe, and a spontaneous left pneumothorax. On three separate occasions, he was bronchoscoped and large casts of tumor that had been protruding from the orifice of the left upper lobe were removed. Subsequently, he underwent left upper lobectomy. The patient's symptoms disappeared following that procedure, and he remained well for more than two years before his death.

Another patient with a known unresectable renal carcinoma of three years'

duration suddenly developed acute respiratory distress; at bronchoscopy the left main bronchus was totally occluded by necrotic neoplastic tissue. The occlusion was somewhat alleviated by removal of a large amount of tissue through the bronchoscope. However, he was extremely desirous of several more months of life for business reasons and elected to undergo pneumonectomy. He lived for six months after pneumonectomy.

A third patient had undergone abdominoperineal resection for adenocarcinoma. Eleven years later he developed intractable cough and shortness of breath. He was found to have multiple bilateral pulmonary nodules with early obstructive pneumonitis in the left lung. He elected surgery, and no lesser procedure than a pneumonectomy could be performed; he was free of pulmonary symptoms until his death seven months later from cerebral metastases.

A fourth patient had Hodgkin's granuloma proved by biopsy of cervical lymph nodes. Eleven years after that diagnosis, she was examined because of a cough that had become progressively more severe and a right-sided wheeze of three years' duration. Roentgenograms showed atelectasis of the right upper lobe. Bronchoscopy then demonstrated a stenosis of the intermediate bronchus on the right side. A totally consolidated right upper lobe was resected, which contained parenchymal Hodgkin's granuloma. Subsequently, the stenosis of the intermediate bronchus was treated with repeated dilatations. However, she continued to have symptoms; six months following the upper lobectomy, she underwent resection of the remainder of the right lung. When last seen, 19 years after the original diagnosis of Hodgkin's granuloma, she was well.

DISCUSSION

One of our prime missions as physicians is to alleviate suffering and this mission is obviously not furthered by operating on disseminated malignancy. Metastatic neoplasm in the lung usually reflects a widely disseminated and hopelessly incurable malignancy. Therefore, in selecting patients for surgery, there must be good cause to anticipate that it will result in worthwhile palliation or cure or resolution of a strong question as to the proper diagnosis. Thoracotomy per se today is associated with low mortality and morbidity; in this series of 38 patients there was only 1 operative mortality. However, the results certainly must be carefully evaluated before this type of procedure can be justified.

As previously mentioned, biopsy as a planned minimal procedure seems worthwhile as a diagnostic measure. It has proved safe and definitive without undue discomfort or inconvenience to the patient. Palliative resections for bronchial obstruction should be undertaken only when the patient is fully cognizant of the limited goal in view. In this series of patients there were nine diagnostic biopsies, four palliative resections, and 25 operations for cure. More than 50 per cent, 14 procedures, of the latter 25 were some type of resection. This is a satisfactory resectability rate for pulmonary malignancy and would

seem to justify such an aggressive approach if there are many long-time survivors.

Of 18 resections performed in the entire group of 38 patients, 4 were palliative, as has been mentioned. Another one of the resections was performed on a patient who was found to have an uncontrollable renal primary neoplasm early in the postoperative period. Thus, 13 of the 18 resections potentially were curative (Table 2). Four of these 13 resections were pneumonectomies, and the remaining nine were lobectomies or lesser procedures. In the pneumonectomy group, there was one operative death; this patient, as has been mentioned, on postmortem examination was found to have had residual disease. Two additional patients died of their disease, 9 and 10 months respectively, following pneumonectomy, and the remaining patient was lost to follow-up two years following surgery. Thus, in this very small group of cases it is hard to justify the use of pneumonectomy in treating metastatic disease.

Table 2. — *Data in 13 potentially curable cases of neoplastic metastasis in the lung, treated by resection*

Type of resection	No. of cases	Operative death	Postoperative deaths	Living
Pneumonectomy	4*	1 (residual disease)	2 (9 and 10 mo. postop.)	—
Lobectomy or lesser resection	9	—	1 (1 yr. postop.)	8 (1—5½ yr. postop.)

**One patient lost to follow-up two years postoperatively.*

On the other hand, among the nine patients who underwent lobectomies or lesser resections and were considered potentially curable, one died within a year after operation and the other eight still are living from one to five and one-half years postoperatively. Among the eight living patients, two have had second thoracotomies for subsequently appearing contralateral metastases.

It is impossible from a series of this size to judge whether a particular type of carcinoma is more suitable for pulmonary resection than any other. Our living patients include: two with hemangiopericytoma, two with carcinoma of the breast, and single patients with renal, ovarian, salivary and colon primaries.

A distinct impression is gained, however, that the duration of time from treatment of the primary neoplasm to treatment of the metastasis is of some

prognostic significance. Almost all of the late metastases occurred in patients who still are living (Table 3).

Table 3.— *Time lapse between treatment of primary tumor and resection of neoplastic metastasis in 13 potentially curable cases*

Time lapse (years)	No. of patients	
	Living	Dead
0	—	1
2	3	1
3	—	1
4	—	1*
5½	—	1
6	1	—
7	2	—
10	1	—
13	1	—
Range 0-13	Total 8	5

**Lost to follow-up after two years.*

As mentioned previously, an assumed pulmonary metastasis may prove to be a primary bronchogenic neoplasm. This situation was exemplified by a patient who had a right radical mastectomy for carcinoma. Four years later, in 1950, she developed a peripheral lesion in the left upper lobe of the lung that continued to enlarge for a number of months despite hormonal therapy. A left upper lobectomy was performed and the lesion was found to be a primary squamous bronchogenic carcinoma. Five years after lobectomy, the patient still is well.

Another facet of the problem of surgical treatment of metastatic disease is that bronchogenic carcinoma frequently metastasizes to the central nervous system. In our experience a surgical approach under these circumstances is very rarely indicated. In fact, aggressive surgery is strongly contraindicated in a patient having proved bronchogenic carcinoma and signs of an expanding intracranial lesion. However, we have operated on two such patients, although in neither of them was more than palliation achieved. One patient had a small superficial nodule of the scalp that on biopsy proved to be metastatic carcinoma. The only other positive findings were minimal prominence of the hilum of the left lung, and on bronchoscopy several atypical cells. Left pneumonectomy was performed, and a month later radical excision of the scalp and skull. The patient died two years after pneumonectomy, of disseminated neoplasm. The second patient had signs of an expanding intracranial lesion; roentgenograms showed a small peripheral lesion in the right upper lobe. He underwent craniotomy with enucleation of a nodule of metastatic adenocarcinoma. Two weeks

later a right upper lobectomy was performed. The patient died of further intracranial metastases 23 months after lobectomy, but for 20 months of that palliative period he had been able to continue working.

Summary

The indications for surgery in patients having metastatic neoplastic disease in the lung are broadly defined on the basis of findings in 38 cases. Surgery is of value as a diagnostic and a definitive therapeutic procedure in carefully selected cases. In 13 of the 38 patients, resection was performed for possible cure of the condition. Eight of those 13 patients still are living, all eight having undergone lobectomies or lesser resections. In our series the late appearance of pulmonary metastases seemed to indicate a more favorable prognosis.

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THE PLACE OF EXTENDED GASTRIC RESECTION IN THE TREATMENT OF GASTRIC MALIGNANCY

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EXTENDED gastric resection is required in some patients if the primary malignant growth is to be removed completely in the hope of cure. An *extended* resection does not necessarily imply *total* gastric resection. It does imply removal of adjacent organs or structures involved by extension of the primary cancer. Enough stomach should be resected to insure the removal of an adequate margin of normal tissue around the tumor; and neighboring structures such as the mesentery of the transverse colon, the transverse colon itself, part of the pancreas with the spleen, or portions of the diaphragm or left lobe of the liver, may be removed en bloc with the stomach. If the patients are properly selected, the results often are gratifying; but if extended operations are used routinely in the treatment of hopelessly advanced malignant disease, cancer is disseminated and nothing but harm is done.

The following cases are illustrative of satisfactory results.

Case 1. (*S.O.H.*) *Survival for 4 years and 363 days after partial proximal esophagogastrectomy with resection of the spleen and portions of the left lobe of the liver, pancreas, and diaphragm.* The patient, a 40-year-old man, had a large tumor involving the entire upper end of the stomach with extension into the diaphragm, the left lobe of the liver, and the hilum of the spleen. The extended resection was undertaken in the absence of distant metastases and because of the comparative youth and good general condition of the patient. Additional diaphragm was removed when frozen section study showed the original line of resection to be close to the tumor. The pathologic report of the tumor was as follows: "Undifferentiated carcinoma of stomach, body and cardia, massive, ulcerating. Marked local extension into wall, to spleen, portion of pancreas, diaphragm."

The patient recovered without complications and did well for about four and one-half years, at which time pain in the back developed and heralded hopeless recurrence. He died after a chordotomy for unremitting pain, just two days short of a "five-year survival." Postmortem examination disclosed retroperitoneal recurrence of cancer.

Comment.—Although he was not cured, the patient had a very satisfactory palliation for more than four years; without resection, survival probably would have been measured in months.

Case 2. (*S.O.H.*) *Well, five years and four months after subtotal gastric resection with simultaneous transverse colectomy.* The patient, a 64-year-old woman, had a huge ulcerating tumor involving the distal two thirds of the stomach with extension into the transverse mesocolon. At operation there was no evidence of distant metastases. An en bloc resection of the stomach, the greater omentum and the involved mesocolon was performed. This compromised the blood supply of the transverse colon, necessitating a transverse colectomy. A feeding jejunostomy and a decompressive tube colostomy supplemented the

resection. The pathologic report was as follows: "Carcinoma of stomach, simplex and poorly differentiated adenocarcinoma types, ulcerating, with 1 of 16 lesser curvature lymph nodes and 3 of 25 greater curvature lymph nodes involved."

The patient is seen periodically; she has developed a cyst of the right kidney but otherwise has remained well without evidence of disease for more than five years.

Comment.—This case represents an unusual instance wherein an invasive tumor with involvement of lymph nodes has responded satisfactorily to surgical excision.

Case 3. (*S.O.H.*) *Well, five years and four months after total gastric resection with simultaneous transverse colectomy, splenectomy, partial pancreatectomy, and resection of a portion of the anterior abdominal wall.* The patient, a 52-year-old man, had a large tumor with a seven-centimeter central ulceration extending directly to the transverse mesocolon and the pancreas. The tumor involved practically the entire stomach, and was adherent anteriorly to the abdominal wall. After it had been determined that there were no distant metastases, en bloc resection was performed, leaving a one-centimeter cuff of stomach at the esophageal end. A Billroth I type of anastomosis was performed, with a supplementary feeding jejunostomy and decompressive tube colostomy. The pathologic report was as follows: "Undifferentiated carcinoma, extensive, of body and pyloric antrum of stomach, rapidly growing, none of 5 lymph nodes involved."

The patient has remained well for more than five years, engaging in his strenuous occupation in a foundry, often working 60 hours a week.

Comment.—The application of the en bloc principle has effected an apparent cure in this patient who seemed to have a very unfavorable tumor.

Case 4. (*G.C., Jr.*) *Well, five years and ten months after resection of huge leiomyosarcoma with apparent extension to the liver, and 19 years after the original exploration for "inoperable" neoplasm.* The patient, a 41-year-old man, had required many transfusions for repeated gastric hemorrhages during a period of 18 years. Tissue from a tumor biopsied but not resected 14 years before, in 1936, was reported as being "undifferentiated carcinoma"; the prognosis was regarded as hopeless. Nine years later, in 1945, the patient was advised to undergo exploration because of a palpable tumor mass and persistent hemorrhages, but he refused surgery. In 1950, through a thoraco-abdominal approach an enormous tumor with regional lymph nodes was removed; the apparent extension to the liver was cauterized with the Bovie unit. There were no distant metastases, but the regional lymph nodes were very large and seemed grossly involved. The pathologic report was as follows: "Leiomyosarcoma, slowly growing, with 2 massive ulcerations; marked sarcoid reaction in lymph nodes without apparent neoplasm."

Since that operation in 1950, the patient has remained well, working 40 hours a week as a foreman in a factory. He has had no more hemorrhages.

Comment.—The long history of illness made it clear that the tumor was slow growing; the resection has proved worthwhile and apparently curative.

Discussion

Realistic surgical treatment of gastric malignancy calls for a clean resection of the primary tumor with an adequate margin of normal tissue. This should be done en bloc without a biopsy, for a biopsy may disseminate cancer. The greater

omentum and the lymph-node-bearing area from the esophagus downward, including the nodes around the left gastric artery, are removed routinely with the stomach. Secondary attention is given to those ill-defined areas of lymphatic drainage which are difficult of access; their involvement by the tumor we believe to be comparable to invasion of supraclavicular nodes by cancer of the breast, and connotes surgical incurability. The nodes in question are those at the porta hepatis or posterior to the pancreas, and fixed nodes about the aorta posterior to the stomach or at the celiac axis.

Before a surgeon commits himself to an extended resection, he should determine whether a cure is within the realm of possibility. It is presumed that in the preoperative survey a roentgenogram of the chest has shown no evidence of metastases, and that physical examination has excluded the presence of supraclavicular nodes, a nodular liver, ascites, or a rectal shelf. If there is clinical evidence of distant metastases, the simplest means for obtaining a tissue diagnosis should be employed—lymph node biopsy, needle biopsy, or cytologic study of ascitic fluid. If tissue diagnosis is positive for metastatic malignancy, further surgery ordinarily is contraindicated.

At operation the surgeon carefully examines both lobes of the liver for hepatic metastases, and searches the peritoneal surfaces for implants. The presence of either is confirmed by frozen section study of a small piece of tissue that has been taken with every precaution to prevent dissemination of cancer. Positive findings ordinarily contraindicate a resection.

Next, the surgeon inspects the undersurface of the transverse mesocolon, a favorite site of extension. Involvement at the root of the mesentery, particularly near the superior mesenteric vessels, precludes a cure. The same may be said for extension along the left gastric vessels and retroperitoneal extension over the great vessels. It may be necessary to divide the attachment between the greater omentum and the transverse colon in order to determine whether there is posterior extension. The surgeon must avoid the pitfall of committing himself to performing a massive resection before discovering that it cannot possibly cure the patient. This error usually is the result of underestimating the degree of extension that exists posteriorly above the pancreas.

If *hopeless fixation* is ruled out, en bloc dissection may be attempted. The surgeon's efforts should be aimed principally at encompassing the primary lesion and its immediate zone of lymph node metastasis. Accessory procedures such as splenectomy should be performed only when they facilitate the operation. Dissection of lymph nodes behind the head of the pancreas or off the hepatic artery, or a dissection about the celiac axis may be performed as adjunctive procedures if conveniently done without increased risk, but improvement in results will be unlikely. If there is no involvement of lymph nodes, these additional dissections are unnecessary; if lymph nodes are involved in those locations, the outlook is so very poor that additional surgery, no matter how extensive, follows the law of diminishing returns and the risk exceeds the probable benefit.

Summary and Conclusions

1. *Extended gastric resection* is defined as en bloc removal of adjacent organs together with an adequate amount of stomach; it is not necessarily a total gastric resection.

2. Extended resection often is justified when no evidence of incurability of the lesion is found.

3. Evidence of distant metastases such as peritoneal implants should be specifically sought: their presence contraindicates an extended resection.

4. Extension of the primary tumor into the root of the transverse mesocolon, into the celiac axis or retroperitoneal tissues, and lymphatic metastases at the porta hepatis or posterior to the head of the pancreas, also contraindicate extended gastric resection.

5. In properly selected patients, extended gastric resection may give good results; four examples are reported.

DENTAL PROTECTION DURING ENDOTRACHEAL INTUBATION

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PROTECTION of the patient's dental structures during surgical procedures is a matter of increasing concern to anesthesiologists. Confidence in the increasing efficacy of muscle relaxants has resulted in greater use of intubation of the trachea—expanding the field of risk and the number of possible complications. Among these complications is damage to the teeth or to dental prostheses, the results of which may be serious. Not only may there be cosmetic disfigurement, but if the patient aspirates a dislodged tooth or fragment there may occur grave pulmonary complications or the surgical procedure may have to be prolonged in order to locate and remove the aspirated object.

Formerly, the presence of porcelain jacket crowns, synthetic fillings, gold inlays, and small bridges were possible contraindications to the use of endotracheal anesthesia. Now, because of the excellent muscular relaxation achieved with the newer drugs and improved technics, these dental conditions have become accepted risks. However, emergency conditions sometimes arise: the airway suddenly is compromised or hypoxia develops—the patient's life is in danger and immediate intubation of the trachea becomes mandatory. To visualize the larynx as quickly as possible, the patient's upper incisors become the pivot point for the laryngoscope (Fig. 1), providing leverage against anterior pharyngeal structures. This force may be so great as to damage normal teeth; but, in this situation, concern for the integrity of the incisor ridge is superseded by the immediate necessity of establishing an airway.

If a tooth or dental prosthesis is damaged and the fragments are lost, the possibilities of serious complications arise. Not only must the cosmetic damage be repaired, but all of the dental fragments must be found. During a difficult intubation or endoscopy, it is not uncommon for a dental fragment to be aspirated with a gasping respiration. Roentgenography of the chest is necessary to locate an aspirated fragment; if it is identified, it must be removed by a further operative procedure. Failure to locate and remove all dislodged dental fragments and the subsequent development of pulmonary disease may form the basis for unpleasant medicolegal action.

Numerous appliances have been recommended to prevent injury to the upper teeth. For many years, endoscopists have used lead shields to prevent damage with bronchoscopes or esophagoscopes. However, these were unsatisfactory, for the hard metal would grind against the brittle dental enamel. Anesthesiologists introduced a tooth protector made of adhesive tape, an ingenious device consisting of three or four thicknesses of zinc oxide adhesive tape with the adhesive side exposed to secure the appliance to the teeth, gums,

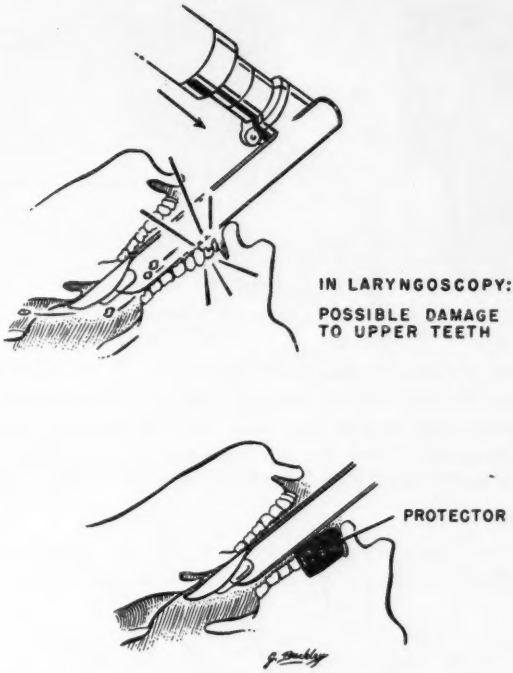

Fig. 1

lips, and skin of the face. The appliance was attached to a string so that if it did slip into the mouth it could be easily retrieved. Unfortunately, the teeth were not adequately protected by this means.

A new device that we have found to be satisfactory is the Greenblum Mouth Protector* (Fig. 2). This adequately protects the teeth and also prevents aspiration into the trachea of any fragments that might possibly become dislodged in the mouth. This protector, made of a medium-hard but pliable rubber, fits firmly over the four incisors and two cuspids of the upper or of the lower jaw and extends from the anterior gingival margin over the teeth; applied to the upper jaw, the protector extends across the hard palate for a few centimeters (Fig. 3). The protector is so designed as to give relatively even distribution of pressure over the dental area. The edges of the incisor teeth are protected by a cushion of soft rubber embedded in the device at the points of contact with the incisor teeth. The place where the laryngoscope rests is reinforced by an additional layer of rubber. When, in spite of the protection afforded to dental

*Greenblum Mouth Protector, Louis L. Greenblum, D.D.S., Van Aken Boulevard, Cleveland, Ohio.

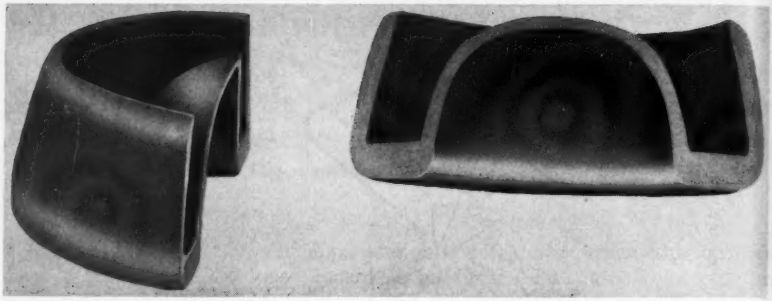

Fig. 2. Enlarged photograph of tooth protector.

structures, teeth or dental prostheses are dislodged or fragmented, the pieces are confined within the cavity of the protector and are removed with it.

Primary teeth begin to lose their roots when the child is about three years of age, and continue to shed through the sixth to the twelfth years, so that they are particularly susceptible to being dislodged during oral surgical or

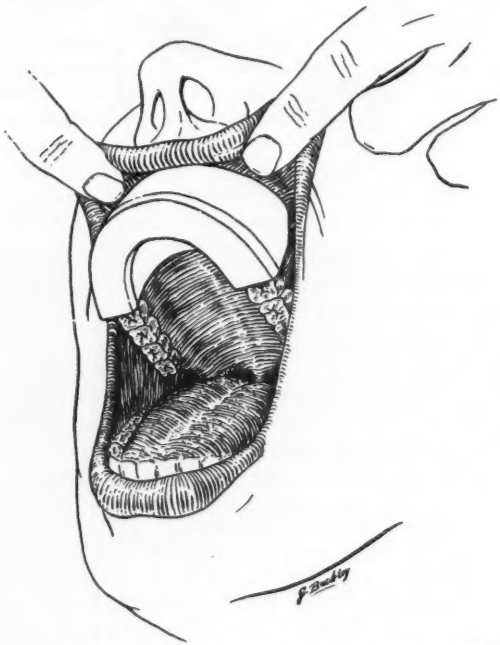

Fig. 3. Application of tooth protector to upper teeth.

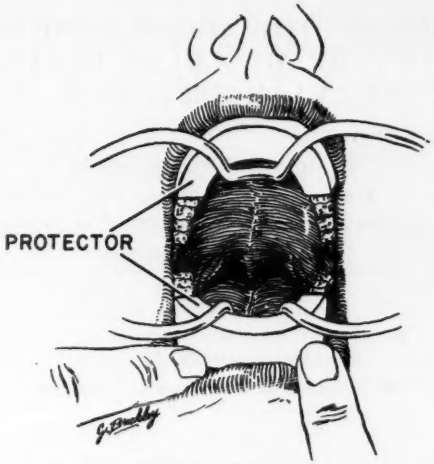

Fig. 4. Protection of the teeth in tonsillectomy.

endoscopic procedures. The small protector, which, because of its basket-like shape retains such dislodged baby teeth in the mouth, is therefore very useful in children (Fig. 4).

Summary

A tooth protector is described which prevents damage to the incisor teeth during intubation or endoscopy.

COARCTATION OF THE AORTA ASSOCIATED WITH A DEFECT OF THE MUSCULAR PORTION OF THE INTERVENTRICULAR SEPTUM IN AN INFANT

A Clinicopathologic Study

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THE association of coarctation of the aorta and a defect of the muscular portion of the interventricular septum has been infrequently reported. Bennetz[1] noted the case of a four-month-old infant who had coarctation of the aorta, patent ductus arteriosus, and large multiple defects of the interventricular septum. Abbott[2] in her review of 200 cases of coarctation of the aorta (adult type) found only one case associated with an interventricular septal defect located in the membranous portion.

Calodney and Carson[3] in their study of 22 cases of coarctation of the aorta in infants had necropsy reports for 21. Of those 21, 9 infants, all having coarctations of infantile type, had associated interventricular septal defects of unstated sites. Most of the nine infants also had other major defects.

We are presenting the clinicopathologic findings in an infant who had coarctation of the aorta (adult type) and a defect of the muscular portion of the interventricular septum.

CASE REPORT

Clinical Features

A 17-week-old boy was admitted to the hospital for cardiac evaluation. He had been a full-term infant weighing seven pounds. No initial respiratory distress had been noted. When he was two weeks old he was taken to the family physician because of impetigo and lack of appetite. At that time respirations were observed to be shallow; no murmur was heard.

When the infant was eight weeks old, he became colicky and respirations appeared to be labored. A roentgenogram of the chest showed a slightly enlarged heart and a large thymus. Roentgen therapy was advised and one treatment was given. After this therapy,

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the parents noted that the breathing had become fuller and more relaxed. Roentgen studies of the infant at 15 weeks showed definite cardiac enlargement.

The family history was not remarkable; two other siblings were said to be in good health.

Physical examination revealed an infant boy who was 57.4 cm. long and who weighed 5550 gm. (12.3 pounds). The rectal temperature was 101.5 degrees F. (38.5 degrees C.); the pulse was 120 per minute, and the systolic blood pressure, 140 mm. Hg. He appeared to be undernourished; the skin was gray. An abdominal type of respiration was noted with inspiratory retraction of the lower rib cage and suprasternal notch. The heart was enlarged. A grade II systolic murmur, heard best in the second and third interspaces at the left sternal border, was transmitted to the left suprascapular area. The second cardiac sound was accentuated at the left sternal border. Bounding brachial arterial pulsations were easily felt bilaterally. The liver was palpable 2 cm. below the right costal margin. No abdominal aortic pulsations could be felt. A faint femoral arterial pulsation was noted and appeared to vary with the respiratory cycle; it was present during prolonged breath-holding and during the phase of expiration. There was no clubbing of the fingers.

Laboratory findings were as follows: Hemoglobin content, 11.5 gm. per hundred milliliters; white blood cell count, 9850 per cu. mm.; fasting blood sugar, 76 mg. per hundred milliliters; and serologic tests gave negative results.

Fluoroscopic findings showed the heart to be more than 50 per cent enlarged and extending anteriorly to the chest wall, suggesting the configuration of a grossly enlarged right-ventricular outflow tract. The cardiac apex was displaced downward to the left, and in the left anterior-oblique view the posterior silhouette extended dorsally to the spine at 65 degrees of rotation. There was increased convexity of the left-ventricular silhouette with no clear-cut evidence of left auricular enlargement. A roentgenogram of the chest showed hilar markings greatly increased in size bilaterally, and the pattern of the peripheral lung fields suggested generalized increased vascularity.

An *electrocardiogram* revealed a gross delay in conduction in leads from the right precordium, with small early r waves and tremendously elevated late secondary r waves. In addition, there was a deeply inverted T wave with a delayed r wave in leads from the left precordium, a pattern suggesting the presence of both right and left ventricular enlargement.

The patient was observed for a seven-day period. On the second day in the hospital his temperature rose to 104 degrees F. (40 degrees C.) but returned to normal. The ventricular pulse rate varied from 140 to 200 beats per minute. During a severe crying spell the child's skin showed generalized mottling and moderate cyanosis. Moist râles were persistently present over both hilar areas posteriorly and in both lung bases. There was a trace of periorbital edema. The patient was treated with Mercuhydrin,* Crystodigin** and aqueous penicillin; the result was an effective diuresis and the loss of 1 kg. (2.2 pounds) in weight.

Cardiac catheterization. On the infant's fifth day in the hospital, catheterization was performed by way of the right superficial femoral artery and vein. The findings are summarized in the Table. Repeated attempts to catheterize a patent ductus arteriosus from the aorta were unsuccessful. An obstruction in the aorta below the left subclavian artery was demonstrated by retrograde aortic catheterization. Venous catheterization revealed the right auricle to be dilated. There was no demonstrable left-to-right shunt at

*Mercuhydrin, Lakeside Laboratories, Inc., 1707 E. North Ave., Milwaukee, Wisconsin.
**Crystodigin, Eli Lilly & Co., 740 S. Alabama St., Indianapolis, Indiana.

the auricular or ventricular levels. The blood pressure in the right auricle and in the right ventricle was abnormally high; the ventricular systolic pressure closely approximated intra-aortic pressure above the coarctation. The systolic pressure in the aorta below the coarctation was substantially lower than the right ventricular systolic pressure, ruling out the possibility of the entrance of the patent ductus arteriosus into the aorta below the coarctation.

Table.—*Findings from cardiac catheterization of right superficial femoral artery and vein*

Sampling location	Blood pressure, mm. Hg	Oxygen content	
		Volume %	% saturated
1. Inferior vena cava	—	3.7	30.8
2. Right auricle	6.2 (mean)	2.8	23.3
3. Right ventricle	118/80	2.7	22.5
4. Thoracic aorta (below left subclavian artery) above coarctation	120/68	4.3	35.8
5. Distal transverse aortic arch above coarctation	110/50	4.7	39.2
6. Left subclavian artery above coarctation	100/49	5.5	45.8
7. Thoracic aorta below coarctation	63/44	5.5	45.8
OXYGEN CAPACITY		12.0	100.0

The circulation time was 4.0 seconds (normal, 4.0 to 6.0) as measured from the right ventricle to the tongue after the injection of 2.5 ml. of fluorescein. Although the circulation time from the right ventricle to the tongue was at the lower limit of normal, it was much shorter than would be anticipated in the presence of congestive cardiac failure. The oxygen content of blood taken from the aorta above and below the coarctation was higher than that found in the right ventricle, but lower than the normal 94 to 96 per cent of capacity. This degree of oxygen unsaturation must have been due in part to a right-to-left shunt at the ventricular or proximal aortic levels and was accentuated by inadequate uptake of oxygen by the lungs in the presence of pulmonary edema.

It was concluded that the child had either an interventricular septal defect or a large patent ductus arteriosus proximal to the coarctation. Since the child's functional status was rapidly becoming incompatible with survival, surgical exploration was indicated.

Surgical procedure. A thoracotomy was performed on the seventh day in the hospital. The heart was found to be enlarged; an incision was made in the pericardium and 15 to 20 ml. of clear straw-colored fluid was removed. During mobilization of the distal aortic arch, profound bradycardia occurred. Intravenous atropine was administered, and a fast but regular pulse was established. No coarctate segment was recognized by direct visualization or by palpation. A large ductus arteriosus, in which arterial pulsations were believed to be palpable, was ligated. The pericardium was opened further to visualize the origin of the aorta. Profound bradycardia recurred, followed by cardiac arrest. More than 30 minutes of cardiac massage was required to re-establish a spontaneous heart beat. The chest was closed after a period of observing the heart beat without the aid of massage.

Twelve hours after surgery, the cardiac rhythm was regular, the ventricular pulse rate being 140 to 160 beats per minute. There were excellent brachial arterial pulsations; strong femoral pulses still were absent. Coarse rhonchi throughout the left lung, a

(a) (b)

Fig. 1. Gross cardiac findings: (a) Interior view of the heart from the right side of the interventricular septum; the probe shows the location of the defect. (b) Partially opened heart; anterior window has been removed to show the prominent bilateral ventricular hypertrophy and the defect in the muscular portion of the interventricular septum.

pericardial friction rub, and a grade II to grade III rough systolic murmur at the left second to fourth interspaces were noted. There was slight periorbital edema and one plus cyanosis. Sixteen hours following surgery, the Moro embrace and the sucking reflexes were present. Twenty hours postoperatively the respirations suddenly ceased and the patient died.

Pathologic Features

The positive findings of the necropsy were limited to the heart and the lungs.

The *heart* weighed 100 gm. and was symmetrically enlarged. The myocardium was reddish brown in color and firm; the endocardium was smooth and glistening. The walls of the right and the left ventricles each measured 1.1 cm. in thickness. The cardiac valves were normal and measured circumferentially: tricuspid valve, 4.5 cm.; pulmonic valve, 3.0 cm.; mitral valve, 3.2 cm.; aortic valve, 2.0 cm. An oval interventricular septal defect, 0.9 by 0.4 cm., was present in the muscular portion of the septum, lying in the anterosuperior area 3.0 cm. from the apex (Fig. 1). The aorta was normally positioned but narrowed from a point just proximal to the origin of the left subclavian artery to immediately distal to the region of insertion of the ductus arteriosus. The ductus arteriosus was widely patent on the pulmonary arterial side but was anatomically closed at its aortic junction. At the origin of the left subclavian artery, the circumference of the aorta was 1.1 cm.; in the region of the ductus it was 0.7 cm.; and just distal to the ductus it was 1.5 cm. The opened aorta possessed a circumferential wedge-shaped area of thickening at the level of insertion of the closed ductus arteriosus, narrowing the lumen to 0.4 cm. in circumference (Fig. 2). Microscopically, sections of this area showed only

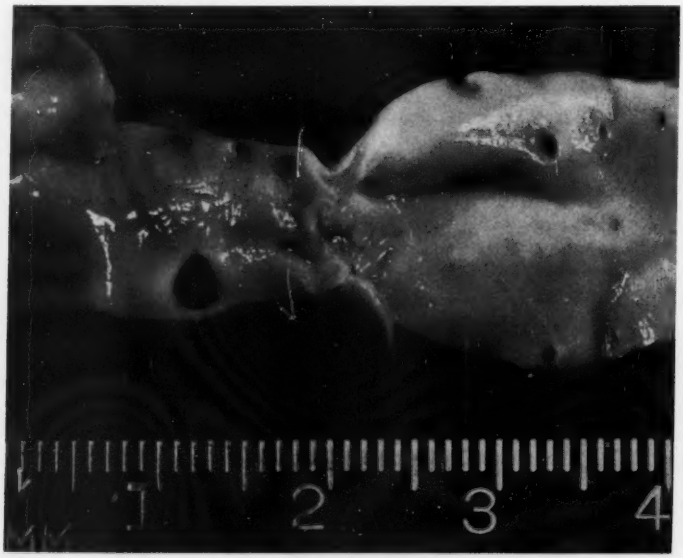
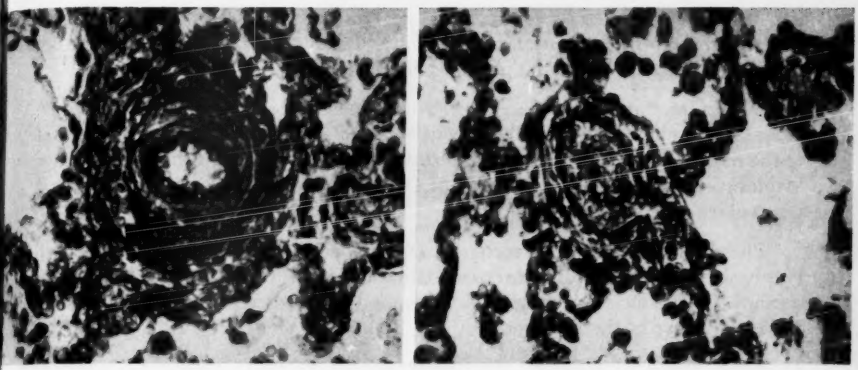


Fig. 2. Opened aorta showing the coarctate annulus of elastic tissue and slight poststenotic dilatation. The puckered insertion of the ligamentum arteriosum is centered in the defect.



(a) (b)

Fig. 3. Histologic comparison of pulmonary arterioles; photomicrographs of: (a) pulmonary arteriole showing muscular hypertrophy and some elastic fragmentation, from infant whose case is reported here; Verhoeff elastic-Van Gieson stain; X270. (b) Normal pulmonary arteriole from infant of same age; Verhoeff elastic-Van Gieson stain; X270.

thickening of the elastic media; there was no intimal change. The pulmonary artery was dilated to a circumference of 3 cm.

The left *lung* weighed 55 gm.; the right weighed 75 gm. The cut surfaces were red and somewhat firm. Tissue sections demonstrated intrapulmonary arteriolar hypertrophy characterized by thickening of the musculature of the media (Fig. 3).

The final anatomical diagnoses were: Congenital heart disease, with coarctation of the aorta (adult type), and interventricular septal defect of the muscular portion of the septum; cardiomegaly; intrapulmonary arteriolar hypertrophy.

COMMENT

Coarctation of the aorta is not commonly a clinical problem in very young persons, unless some associated difficulties are present. These associated problems include patent ductus arteriosus, intracardiac anomalies, intercurrent infection, or the development of an ectopic tachycardia. Our case was characterized clinically by stunted growth and development, and congestive failure. The infant's heart working against the resistance of the coarctate segment apparently functioned as though it were a three-chambered organ because of the interventricular septal defect. As a consequence, generalized myocardial hypertrophy and insufficiency resulted.

The apparent evidences of a right-to-left shunt, manifested by oxygen desaturation and possible shortening of the circulation time, strongly suggest shunt-reversal in the presence of myocardial failure. It is obvious that the shunt of blood originally must have been left to right and became intensified by the increased resistance, offered by the coarctation, to blood being ejected from the

left ventricle. The hypertrophic changes in the intrapulmonary arterioles probably represent a retention of fetal characteristics functioning as a protective mechanism against the pulmonary hypertension.

Intrapulmonary arteriolar hypertrophy has been reported by Edwards, Douglas, Burchell, and Christensen[4] in a case of coarctation of the aorta distal to the mouth of the patent ductus arteriosus. In a similar case, Johnson, Ferencz, Wiglesworth, and McRae[5] found that principally the small and medium-sized pulmonary arteries were involved.

The difficult problem of recognizing the coarctate segment at surgery well emphasized how subtle the external manifestations of the lesion can be in early infancy. The associated arrhythmia curtailed the surgeon's efforts to establish the true nature of the disorder.

Summary

An unusual case of coarctation of the aorta associated with an interventricular defect of the muscular septum has been presented. The presence of the latter defect is believed to be responsible for the patient's developing cardiac decompensation early in infancy.

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CHRONIC ULCERATIVE COLITIS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Report of a Case

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THE occurrence of both chronic ulcerative colitis and systemic lupus erythematosus in the same patient has not to our knowledge been previously reported in the literature. At about the time we saw a patient in Cleveland with both diseases, Boone and McKee[1] in Toronto reported to us that they had observed and treated a similar case.

There is some evidence that chronic ulcerative colitis may be one of the collagen diseases, similar to lupus erythematosus. Levine, Kirsner, and Klotz[2] noted an absence of the homogeneous ground-glass substance of the basement membrane of the epithelial cells of the rectal mucosa in patients with chronic ulcerative colitis. They report: "The epithelial cells of the mucosa were morphologically intact . . . , but in many areas the mucosa had separated from the underlying connective tissue. In the intervening space a homogeneous, Hotchkiss-positive, metachromatic material was observed. Such areas were often free of inflammatory response." This metachromatic material was not present in a patient with active amebiasis and active inflammation or in a patient with lymphopathia venereum and active colitis. Finally, they found that biopsies in patients with ulcerative colitis who had received ACTH therapy showed areas in which the ground-glass substance of the basement membrane had returned. Warren and Sommers[3] have described a vasculitis resembling periarteritis nodosa or thromboangiitis obliterans in some patients with chronic ulcerative colitis. These two studies[2,3] suggest that chronic ulcerative colitis may be a systemetic, connective tissue or collagen disease similar to systemic lupus erythematosus, rather than a local infection of the colonic mucosa.

The occurrence of erythema nodosum, rheumatoid arthritis, iritis, and glomerulitis in association with ulcerative colitis suggests the aforementioned possibility of an etiologic relationship. Frequently these systemic complications

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become worse with an acute flare-up of the colitis, and subside as the colitis improves. Because of the similarity in some respects between chronic ulcerative colitis and systemic lupus erythematosus, and because of the apparently infrequent coexistence of the two conditions, we believe that this report of our patient having both diseases will be of interest.

Case Report

A 16-year-old girl was first examined on May 2, 1955; she had had frequent watery stools and abdominal cramps for the previous seven years, and bloody stools during the previous four years. In 1952, a barium enema examination, elsewhere, led to a diagnosis of ulcerative colitis. She had had severe anemia requiring four blood transfusions in 1951 and again in 1954. Episodes of fever occurred intermittently with a flare-up of colitis and arthritis. In the summer of 1954, she developed migratory joint pain, swelling, and joint tenderness for which she was given hydrocortisone, 40 milligrams daily. She continued to have diarrhea with three to ten loose stools daily. Occasionally, blood was present in the stools.

On physical examination the patient appeared to be malnourished, weighing only 92 pounds. The only significant findings were the fusiform swellings of the proximal joints of the hands, tenderness of the left knee, and numerous subcutaneous nodules typical of those found in patients having rheumatoid arthritis. There were apical and basal systolic murmurs (grade II) and some cardiac enlargement consistent with mitral insufficiency.

Pertinent laboratory findings were: hemoglobin, 12.1 gm. per hundred milliliters; white blood cells, 9300 per cu. mm. with 20 per cent eosinophils; sedimentation rate 1.75 mm. per minute; bromsulfalein dye, 14 per cent retention in 45 minutes; Wassermann and Kahn test results, negative; cephalin-cholesterol flocculation test, 4 plus; thymol turbidity, 20 units; urea clearance rate, 56 per cent in the first hour and 73 per cent in the second hour; blood urea, 24 mg. per hundred milliliters. All stools were negative for parasites. The agglutination test for dysentery organisms was negative; stool culture was negative for pathologic organisms. The Tiselius electrophoretic protein pattern was: albumin 2.66, alpha globulin 0.61, beta globulin 1.49, and gamma globulin 2.76 gm. per hundred milliliters. The tests for lupus erythematosus (L. E.) (peripheral blood,[4] plasma-dog[5]) all were positive.

A proctoscopic examination disclosed a thickened and granular mucosa with fine ulcerations consistent with chronic ulcerative colitis and a fissure in ano. Barium enema examination showed ulcerative colitis that involved the entire colon and terminal ileum. A roentgenogram of the chest showed cardiac enlargement (left ventricular) and minimal bilateral pleural effusion.

The patient was treated with diet, hydrocortisone (20 mg. twice daily), chloroquine, Azulfidine,* Pyrodoxine, and isoniazid. On May 20 she was passing four stools a day but continued to have pain in the joints. On July 23 the arthritis had improved but she stated that she was unable to tolerate the Azulfidine.

She was seen again August 8 at which time the presenting complaint was a sudden pain in the right lower quadrant of the abdomen, nausea and vomiting, and increase in the diarrhea. Her temperature was 102 degrees F. There was a tender mass in the right lower quadrant. She was admitted to the hospital and treated with prednisone, 10 mg. three times daily, and with penicillin, 600,000 units daily. She improved daily; there was less diarrhea and the mass diminished in size. She was discharged from the hospital on

Azulfidine, Pharmacia Pharmaceutical Co., 270 Park Ave., New York, N.Y.

August 16, eight days after admission, and was advised to take prednisone, 5 mg. three times daily, and penicillin, 600,000 units daily.

When seen on August 23 she was making satisfactory progress. By September 21 she daily was having two to four stools without blood. She continued to take prednisone and she was allowed to go to school on a half-time schedule. On October 3 she was having only two stools daily; hemoglobin was 12.4 gm. per hundred milliliters and the L.E. test was negative; her weight was 98 pounds, and she was attending school on a full-time schedule without difficulty.

Discussion

Our patient had systemic disease with rheumatoid arthritis, cardiac involvement (mitral insufficiency), lupus erythematosus, and chronic ulcerative colitis. The diverse and distinct signs and symptoms, namely those of arthritis, lupus erythematosus, and colitis, responded to steroidal therapy and supplemental measures; with these the arthritis cleared, the L. E. test became negative, and the diarrhea subsided.

Boone and McKee's[1] patient had ulcerative colitis, lupus erythematosus, and evidence of hepatic dysfunction and portal cirrhosis with markedly enlarged liver and spleen. In our patient the positive cephalin-cholesterol flocculation and thymol turbidity tests may reflect changes in the serum proteins that are due to the lupus erythematosus rather than to hepatic dysfunction, although the increased bromsulfalein retention suggests impaired hepatic function. The impaired hepatic function may be secondary to the ulcerative colitis, resulting in chronic diarrhea, negative nitrogen balance and the loss of large amounts of protein in the stool.

The similarities in the two conditions already discussed and the association of both diseases in one patient might suggest a common etiologic factor. However, if there were a common etiologic factor in both conditions, one would expect both diseases to occur frequently in association. To see whether we were overlooking latent lupus erythematosus, tests for lupus erythematosus were performed in 20 other patients with chronic ulcerative colitis. These were negative. Since there is no published report heretofore, and we know of only the one other patient having both conditions,[1] the incidence of the coexistence of chronic ulcerative colitis and systemic lupus erythematosus seems to be no greater than that which would be expected by chance.

Although ulcerative colitis and systemic lupus erythematosus rarely appear together, further studies concerning their possible relationship appear indicated. We believe that L. E. tests should be done in all patients having ulcerative colitis who exhibit any systemic complications, such as arthritis, iritis, or erythema nodosum.

Summary

Ulcerative colitis and systemic lupus erythematosus have much in common. The similarity in regard to the absence of the homogeneous ground-glass

substance, the vasculitis in some patients and the systemic complications all suggest that ulcerative colitis as well as lupus erythematosus may be a systemic collagen disease.

The association of ulcerative colitis and lupus erythematosus is uncommon; we know of only two cases—our own and the one of Boone and McKee.[1] In our patient, chronic ulcerative colitis, lupus erythematosus, rheumatoid arthritis, and mitral insufficiency coexisted. The possibility of a common etiologic factor in ulcerative colitis and lupus erythematosus is only a matter of speculation at the present time.

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DIABETOGENIC ACTION OF PITUITARY

Clinical Considerations

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CLINICIANS are becoming aware that knowledge of the various factors affecting carbohydrate metabolism is important to a better understanding and better control—perhaps eventually the cure—of diabetes in the human being. Although the faulty carbohydrate metabolism that characterizes diabetes mellitus most frequently is traceable to dysfunction of the pancreas and resultant deficiency of insulin, other factors also play important roles in carbohydrate metabolism and their action sometimes causes diabetes or affects an existing diabetes.

Pituitary hormones and other hormones related to pituitary and to adrenal function are parts only of a total complex having intimate connection with carbohydrate metabolism and with hyperglycemia. It appears that hyperglycemia, if sufficiently great or sufficiently long-lasting, in some people may precipitate lasting diabetes and eventually true insulin deficiency; very rarely, hyperglycemia may produce diabetes that is severe and temporary, as in the case reported by Del Greco and Scapellato.[1] The purpose of this paper is to review from the clinical aspect, relationships of pituitary and adrenal factors related to carbohydrate metabolism, in order to reveal some of the complexities of that metabolism and perhaps to gain more insight into means of reversing diabetes.

THE PITUITARY

The pituitary hormones that we think of as being responsible for the onset and persistence of some cases of diabetes in patients are: *growth hormone*, which operates in acromegaly; *adrenocorticotropic hormone* (*ACTH*) at fault in rare cases of pituitary tumor associated with Cushing's disease; and possibly another, "*the Cori factor*" that has bearing on hexokinase activity—it may be neither ACTH nor growth hormone.

Hyperpituitarism and Diabetes

Acromegaly: The diabetes of acromegaly is the clinical counterpart of experimental diabetes that is caused in animals by giving growth hormone. It

From an address presented at a meeting of the New York Diabetes Association, October 27, 1955, New York, New York.

is not possible to state with certainty in a given case whether an excess of growth hormone is the sole responsible factor, or whether this acts together with some excess of ACTH with excess of corticosteroids. Large adrenal cortices commonly have been found in acromegaly, and the studies by Venning and Browne[2] indicate that increased excretion of corticosteroids may occur. If excess ACTH is produced in acromegaly, one would expect the frequent development of Cushing's syndrome, but the two conditions rarely coexist. One case is reported by McCormick and associates.[3] Most observers are dissatisfied with the methods currently available for the estimation of excess corticosteroids, and those methods most recently developed have not yet been fully evaluated for acromegaly. It is to be hoped that the new methods of Sydnor and Sayers[4] for the determination of ACTH in blood will help to solve this part of the problem.

The incidence of diabetes in acromegaly has been variously estimated. The most frequently quoted figure is that of Coggeshall and Root[5] who reported that of 153 acromegalic patients, 35 per cent had glycosuria and 17 per cent had diabetes. We think it is fair to assume that many more than 17 per cent would have been classed as diabetic if glucose tolerance tests had been performed for all. It may be pertinent, however, that ACTH and cortisone cause glycosuria before hyperglycemia occurs as a result of their action.[6] Certainly it is not easy to relate the experimental facts with the low incidence of diabetes in acromegalic patients.

In our series of 76 acromegalic patients, 21 (28 per cent) were classified as diabetic. From the higher incidence it seems evident that mild diabetes, disclosed only by a glucose tolerance test, is present in many acromegalic patients or becomes clinically manifest.

The time lapse between the development of the first signs of acromegaly and the development of those of diabetes varies widely according to available figures. In Coggeshall and Root's[5] series, the time lapse ranged from 1 to 22 years and the findings of Goldberg and Lisser[7] are similar. Of the Clinic series of 21 acromegalic diabetic patients, in one patient the two conditions were diagnosed simultaneously, and in another there was a time lapse of 15 years between the diagnosis of acromegaly and that of diabetes; in the remainder, the time lapse ranged between these extremes.

Diabetes is said to occur much more commonly in women with acromegaly than in women in general. In our series there were 9 women and 12 men who were diabetic and acromegalic. In Coggeshall and Root's[5] series, the diabetes was much more common in those acromegalic patients who had family histories of diabetes.

Usually the diabetes that occurs in acromegalic patients is mild (Table 1), but severe diabetes does occur. In Coggeshall and Root's series, of the 16 patients who died, three died in diabetic coma. None in our series have had diabetic coma. Insulin resistance seems to occur more frequently in acromegalic diabetic patients than in the average diabetic patient; however, there are no accurate statistics to support this impression. We have under observation one acromegalic patient, a 48-year-old man, who requires a maintenance dose of

160 units insulin per day. Two other patients have required 220 and 175 units daily for brief intervals, but the usual requirement is in the range of 60 to 80 units.

Table 1.—Blood sugar levels in 20 acromegalic diabetic patients

Patient no.	Blood sugar, mg./100 ml.		Insulin,* units	
	Fasting	P.C.		
1	224	—	110 PZI	30 R
2	348	—	120 PZI	100 R
3	152	—	10 PZI	
4	285	—	—	
5	147	—	—	
6	188	—	10 PZI	
7	234	—		98 R
8	182	—	—	
9	—	294 (1 hr.)	—	
10	143	—	—	
11	165	—	65 PZI	10 R
12	366	213 (1 hr.)	—	
13	—	202 (1 hr.)	—	
14	—	168 (3 hr.)	—	
15	212	—	—	
16	234	—	—	
17	—	246 (2 hr.)	—	
18	342	—	66 PZI	10 R
19	186	—	—	
20	147	—	—	

**PZI—protamine zinc insulin; R—regular insulin.*

The muscular wasting of acromegaly and the signs simulating amyotrophic lateral sclerosis do not parallel the severity of diabetes. The muscular weakness may be extreme, or actual amyotrophic lateral sclerosis may be present with

very mild or no diabetes, or diabetes may be severe with no evident muscular wasting or weakness.

Diabetic retinopathy has been reported as occurring in acromegaly.[4] We have seen typical diabetic retinopathy in 3 of 21 acromegalic diabetic patients. One of the patients was a man who had had acromegaly for 12 years and diabetes for 8 years at the time retinal changes were first seen. His blood pressure was 160/100 mm. Hg. In another patient a few punctate hemorrhages were found; he was known to have had diabetes for only two years. His blood pressure was 110/60. The third patient was a 28-year-old man who had retinal hemorrhages that were actively recurring; he had been acromegalic for 10 years. He had had improvement in visual fields and apparent slowing of acral growth after removal of a pituitary tumor in 1944. However, he developed diabetes two years later —which was five years before retinopathy was found. His blood pressure was 120/90 mm. Hg. The type of renal failure seen in chronic diabetes, if it occurs, has not been recognized in our acromegalic patients. The paucity of cases of generalized vascular disease with renal failure may be related to the fact that most acromegalic patients die before their primary disease has lasted 15 years and that diabetes in them usually has existed for a much shorter time.

It is mentioned frequently in the literature that there is unusual variability in the severity of acromegalic diabetes. In a sense this is true, but in my own experience in watching the progress of acromegaly for years I have been more impressed by the fact that in most such patients the diabetes is mild and peculiarly stable—vastly different in this respect from the diabetes of so many patients in whom we struggle daily to try to attain adequate control. It is equally true, however, that diabetes may show ingravescence during maintained pituitary hyperfunction, and slow or sudden amelioration with decline in hypophyseal function. However, Darragh and Shaw[8] reported the development of diabetes in acromegalic patients despite the apparent arrest of the acromegaly subsequent to roentgen treatment of the pituitary.

Almy and Shorr[9] reported the development of mastoiditis and basilar meningitis in a 40-year-old man who had had diabetes and acromegaly for five years. He had required 60 units of insulin daily. When evidence of pituitary failure developed, the glucose tolerance became normal and remained normal for five years. John[10] reported the spontaneous disappearance of diabetes in a patient having acromegaly.

Balfour and Sprague[11] reported the case of an acromegalic patient who had had blood sugar levels as high as 384 mg. per hundred milliliters and had required 62 units of insulin daily. Following roentgen therapy directed at the pituitary, an acute episode occurred that was thought to have resulted from rupture of an intrasellar tumor. Subsequently, 10 units of insulin daily controlled the blood sugar at a level of 147 mg. per hundred milliliters.

Recently, Gurling[12] in London reported the case of a 49-year-old acromegalic man who had diabetes with blood sugars as high as 740 mg. per hundred milliliters and mild acidosis with severe coma and fever. The hyperglycemia was controlled with therapy. The temperature continued to rise, the coma continued,

and the patient died. Hypoglycemia in this instance apparently did not develop, although death was associated with pituitary necrosis.

In our own experience[13] reversal of diabetes in acromegaly has been seen to follow long-continued therapy with estrogen. Of six acromegalic women, five had diabetes mellitus. In all it was mild, according to glucose tolerance tests. Very large doses of estrogen were used. Stilbesterol was given in doses of 10 to as much as 50 mg. per day or ethinyl estradiol 1.0 to 5.0 mg. per day, which is 20 to 100 times the usual dosage. The changes were slow, taking months to occur. Although the patients were not on carefully regulated diets we believe that the changes are significant because they were progressive; they were consistent in all five patients and in addition, after the glucose tolerance had become normal or nearly normal during therapy, cessation of treatment was followed in three cases by a recurrence of abnormal glucose tolerance (Fig. 1). That

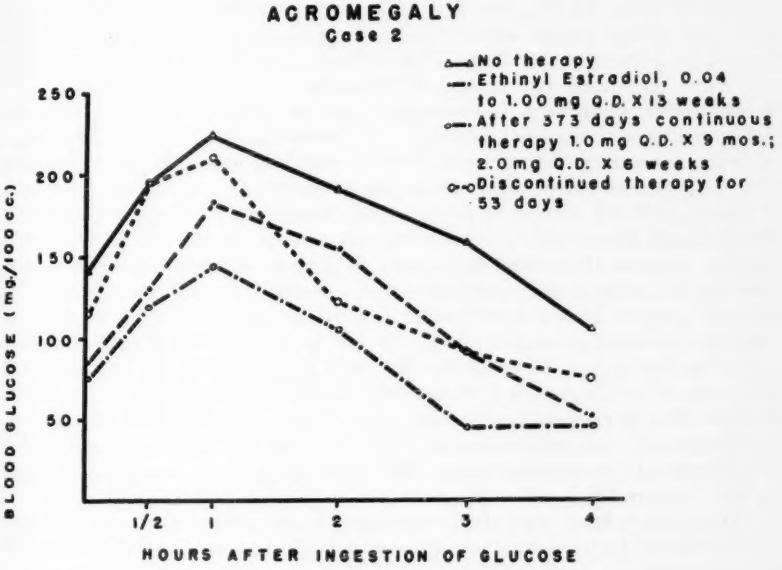


Fig. 1

estrogen suppressed growth hormone production was indicated by soft-tissue shrinkage and a sustained lowering of blood phosphorus levels. The change in glucose tolerance, I believe, was due in part at least to diminished production of growth hormone and the sequence of events tends to confirm animal tests by a clinical experiment.

The effect of growth hormone upon diabetes in the human being has been studied in one patient by Kinsell, Balch, and Michaels.[14] A "highly purified" growth hormone preparation was used. Under controlled conditions this caused

an increase in hyperglycemia and glycosuria and there were minimal evidences of ketonuria. The nitrogen balance changes also were minimal. The authors thought that these findings favored the idea that the effect of growth hormone was one that resulted more from interference with the utilization of insulin than from gluconeogenesis from protein breakdown.

In our laboratories we currently are measuring growth hormone by a method that measures purified pituitary extract in amounts as small as 5 micrograms. The test object is a hypophysectomized rat. The animal is given a standardized dose of radioactive sulfur, the theory being that sulfur is incorporated as sulfated chondroitic acid in the growing epiphysial cartilage. By this means it is hoped that we may study conditions in which an excess of growth hormone occurs, and that such a test may elucidate the relationship of growth hormone to clinical diabetes. Segaloff and associates[15] have recently reported success in measuring growth hormone by another procedure in small amounts of human plasma.

Studies along this line have been reported by Randle[16] in England. He has measured plasma-insulin activity in acromegaly. In regard to an assay for insulin, he points out that if the alloxan-diabetic hypophysectomized adrenalectomized rat is used, one actually is measuring a balance of effects of insulin versus insulin antagonists. For example, when an excess of glucagon, or some other substance that causes a relative insulin-immunity, is present, the assay indicates less insulin than actually is in the solutions tested. Randle[16] believes that if the glucose uptake of the rat diaphragm is used as a test object, glucagon, if present, will not interfere with the insulin measurement. Using this method, he measured insulin-like activity in normal persons, in diabetic and in acromegalic patients. He showed that a diabetic patient receiving insulin had more measurable insulin in the plasma than had a normal person. Plasma from acromegalic patients showed great insulin activity; in fact, measurably more than that usually found in normal plasma diluted up to 100 times. Randle substantiated his findings by showing that he could measure amounts as small as 2 milliunits of insulin as such and, moreover, that he could measure an increased insulin effect in normal plasma diluted four times and collected two and one-half hours after oral administration of glucose. At that stage the plasma contained not only more insulin than it did in the fasting state, but about as much as was measured as 2 milliunits.

Daughaday, Perry, and MacBryde[6] reported an increase in urinary "cortin" as determined by the formaldehydrogenic method in their acromegalic patient having insulin-resistant diabetes.

Hypopituitarism and Diabetes

It is now 32 years since Olmsted and Logan[17] called attention to the fact that pituitary activity has a striking effect on animal sensitivity to insulin, and it is nearly 20 years since Houssay[18] reported his now-classical experiments on carbohydrate metabolism. Severe anterior pituitary failure superimposed on diabetes in the human being is a rare occurrence: perhaps a dozen outstanding cases have been reported.[19-27] It is remarkable that although the general effects

Table 2.—Summary of results of hypophysectomy in 26 patients having severe retinal and renal disease of diabetes mellitus

Table 2.—*Summary of results of hypophysectomy in 26 patients having severe retinal and renal disease of diabetes mellitus*

Author	No. of patients	Length of postop. follow-up (mo.)	Deaths (no. of patients)	Hypertension		Albuminuria		Insulin required		Retinopathy	
				Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Kinsell et al.[29,30]	6	up to 18	2(?)	Present	Absent	+	less	+	much less	4+	4+(?)
Luft et al.[31,32]	20	3—43	7	Present	Absent	+	less	to more than 60 U.	less than 15 U.	4+	Visual acuity improved in 7 patients

of Simmonds' disease were severe in all of the patients, the effects on pre-existing diabetes differed markedly. In one patient a glucose tolerance, previously diabetic in type, became normal[23]; and in another the insulin requirement decreased from 60 to 43 units per day.[24] At the other extreme, there are those who develop hypoglycemia. In one patient "excessive glycosuria" disappeared after acute pituitary necrosis[25]; blood sugar levels fell to 31 and finally to 20 mg. per hundred milliliters. Another patient who had been taking 35 units of insulin daily, discontinued this dosage as pituitary cachexia developed; she died in hypoglycemic crisis.[19] Another patient who had required 60 units of insulin daily, had a similar course: after pituitary necrosis, hypoglycemic crisis developed; she died despite the intravenous administration of 60 grams of glucose.

In instances of severe pituitary deficiency, sensitivity to insulin is very much greater than that seen in Addison's disease. This extreme sensitivity is dramatically illustrated in the case reported by Herstmann.[28] His patient was given intravenously a test dose of 8 units of insulin; she developed hypoglycemic coma and died, despite intravenous administration of glucose. Patients with hypopituitarism may have hypoglycemic reactions from as little as one unit of insulin given intravenously.

Hypophysectomy: Much interest centers about the effect of hypophysectomy on diabetes mellitus since Poulsen[21] observed the disappearance of all evidence of diabetic retinopathy in a 37-year-old woman after she had developed Simmonds' disease. The ocular signs consisted of punctate hemorrhages as well as larger retinal hemorrhages appearing as spots or stripes. There were a few remaining evidences of retinopathy four years after the development of cachexia. After seven years all evidences of that complication seemed to have disappeared.[21] Since that time, hypophysectomy has been performed upon some patients with diabetes, in an attempt to halt the progress or to alleviate degenerative disorders, particularly retinopathy. To date, the results have not been very encouraging.[29-32] A brief summary of the results that have been reported in some patients is presented in Table 2.

Cobalt Teletherapy: Recently we have attempted to produce hypopituitarism in patients having diabetes associated with severe retinopathy, by irradiation (exceeding 10,000 r) to the pituitary. Cobalt teletherapy was used. As yet, we have produced no measurable pituitary deficiency. Except in patients having acromegaly, there has been no significant fall in insulin requirements, blood sugar levels, or urinary steroid titers (Figs. 2 and 3).

PITUITARY-ADRENAL FUNCTION AND DIABETES

Three types of diabetes seen clinically are traceable to adrenocortical action: (1) that which begins with pituitary hyperactivity, such as in cases of pituitary tumor, excess adrenal stimulation, and Cushing's disease; (2) that which is seen in Cushing's syndrome or after exogenous cortisone—it appears to be identical with the first type except that it originates in the adrenal itself,

BLOOD SUGAR AND INSULIN DOSE AFTER COBALT TELETHERAPY 12,000 r TO THE PITUITARY IN DIABETES MELLITUS

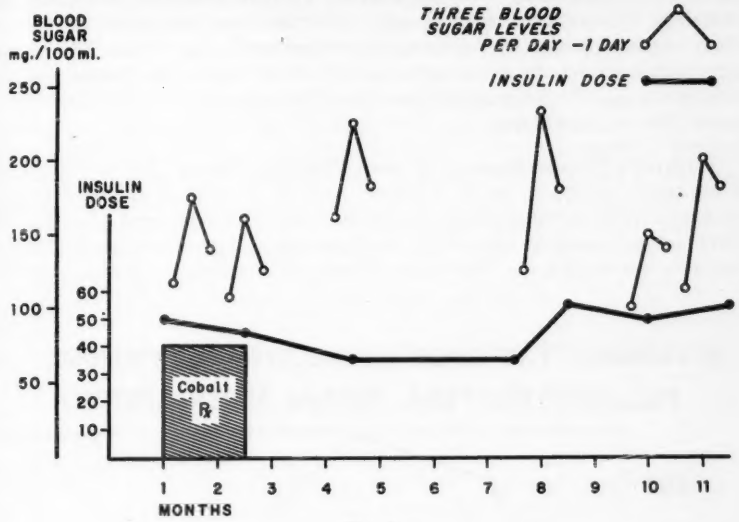


Fig. 2

COBALT TELETHERAPY 12,000 r TO THE PITUITARY IN DIABETES MELLITUS

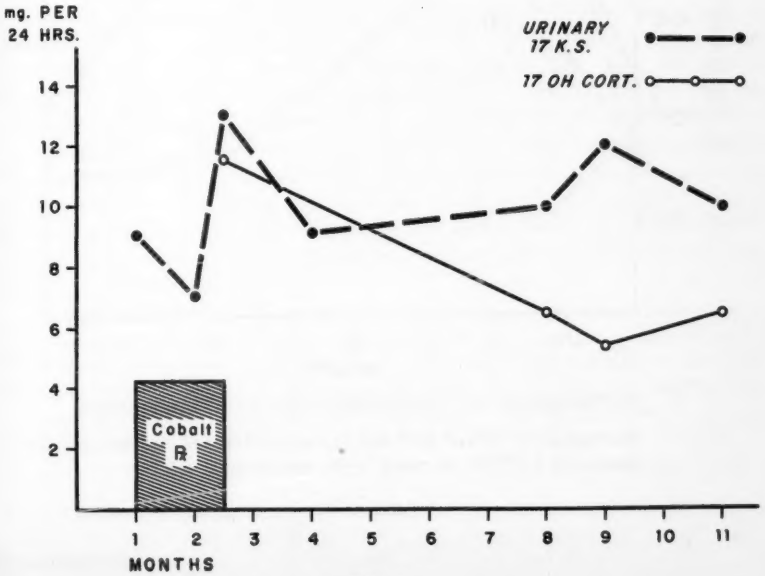
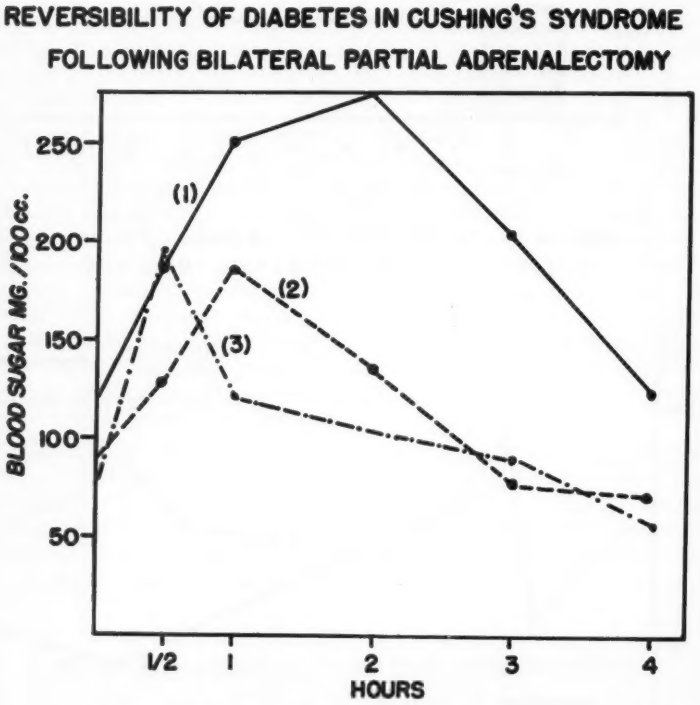


Fig. 3

and in most cases the diabetes is reversible; (3) that caused by an aldosterone-producing tumor. This latter is apparently rare: my associates and I have observed three patients with proven aldosterone-producing tumor. Two of these patients had mild diabetes and after removal of the tumor, the glucose tolerance became normal. There is no clear evidence that pituitary function controls the production of aldosterone.

Cushing's Disease Emanating from Pituitary Tumor: Figure 4 is a chart of glucose tolerance curves in a patient who had typical Cushing's syndrome associated with adrenocortical hyperplasia and who recovered after subtotal adrenalectomy. The reversal of the hyperglycemia is shown by repeated glucose tolerance curves (Fig. 4). Instances of this type in which the disease emanates



(1). Preoperative. (2). Two months postop. (3). 1½ years postop.

Body weight at time of first test, 122 lbs.; at time of last test, 108 lbs. Glycosuria 1.23 gm. on preop. tests; none on postop. tests.

Fig. 4

from pituitary tumor usually are classified as *Cushing's disease*; however, they are rare. One of our patients had typical clinical Cushing's disease with pituitary tumor; the tumor was visualized roentgenographically and was proven at surgery. Presumably the diabetes, which was very mild, was caused by an excess of ACTH. The diabetes disappeared after local application of radioactive cobalt to the pituitary gland. Results of glucose tolerance tests before and six months after cobalt irradiation are presented in Table 3. Diabetes subsequently recurred and adrenalectomy was performed, but the patient died. He had a malignant adenoma of the pituitary.*

Table 3. — *Results of glucose tolerance tests before and after cobalt teletherapy*

Relation to treatment	Blood sugar, mg./100 ml.					
	Fasting	Time, hours p.c.				
		½	1	2	3	4
Before treatment	138	240	370	275	116	—
Six months after treatment	137	208	149	110	75	86

Hyperglycemia after Administration of ACTH: Dustan, Corcoran, Taylor, and Page[33] have shown that in patients with essential hypertension the injection of ACTH may cause hyperglycemia. Cohn and Kolinsky[34] have shown that temporary diabetes mellitus may appear after the use of relatively large doses of corticotropin.

In 1953, Zimmerman, Parrish, and Alpert[35] reported the effects of injections of 40 to 100 mg. of ACTH daily for 5 to 12 days in 17 patients with various conditions, only one of whom had diabetes mellitus. The responsiveness to insulin was measured by the glucose-insulin tolerance test. In this group there were only four patients in whom there was a significant loss of insulin sensitivity.

Recently Martin and Pond[36] cited a case of pituitary insufficiency in diabetes and showed that here, where apparently ACTH was lacking, as judged by extremely low levels of urinary steroids, the administration of ACTH caused a striking increase in insulin requirement and a considerable increase in glycosuria.

The administration of ACTH may have caused lasting diabetes in the case reported by Bishop and Glyn.[37]

Spontaneous Steroid Diabetes: Steroid diabetes arising spontaneously is due to excessive production of hydrocortisone-like compounds by the adrenals. Those hormones cause glycosuria partly by decreasing the ability of renal tubules to reabsorb glucose.[38] They also interfere with the action of insulin, and cause glycosuria and hyperglycemia by impairing carbohydrate utilization and by augmenting the breakdown of protein. Clinically, such diabetes is relatively mild and insulin-insensitive, and is associated with a negative nitrogen balance

**A patient of George J. Hamwi, M.D., Columbus, Ohio.*

that is not fully corrected by insulin. The diabetes usually disappears after the steroid excess has been corrected.

It is a remarkable fact that diabetes does not always occur in patients having severe Cushing's syndrome of long standing. Evidently, important protective homeostatic mechanisms are functioning in these cases and prevent the development of diabetes. We also have seen one patient who clinically had the adrenogenital syndrome with severe alkalosis but without diabetes.

Of 34 of our patients having Cushing's syndrome, 21 (15 women and 6 men) had diabetes. Insulin in dosages ranging from 8 to 90 units daily was prescribed for 7 of the 21 patients.

In patients having Cushing's syndrome it is difficult to ascertain a diabetic origin of vascular complications since the hypertensive disease is an integral part of the condition.

Among our 21 patients with Cushing's syndrome, three had retinopathy. One of the three patients had a hemorrhagic retinopathy not typical of diabetes, and the blood pressure was 175/120 mm. Hg. The remaining two patients had what was classified as *diabetic retinopathy*.

The possibility that certain chemical features of the diabetes associated with Cushing's syndrome are different from those in the average case of clinical diabetes has been studied by Hills, Power, and Wilder.[38] They found that in 34 patients having typical mild diabetes without Cushing's syndrome, the blood lactate and pyruvate levels were not distinctly abnormal. In contrast, in four of six patients having diabetes mellitus and Cushing's syndrome, the blood lactate and pyruvate levels were markedly elevated before the administration of glucose for a glucose tolerance test and rose still further after the administration of glucose. Two of the six patients had hypokalemic hypochloremic alkalosis.

As mentioned previously, long-standing steroid diabetes may not cause permanent diabetes. For example, in one of our patients who had a glucose tolerance of diabetic type before adrenal surgery, the diabetes not only disappeared postoperatively when adrenal insufficiency supervened but the glucose tolerance became that typical of Addison's disease. (Two of our patients in whom adrenal surgery provided complete clinical recovery from severe Cushing's syndrome, developed severe myocardial infarction ten years postoperatively.)

The fact that the steroid diabetes of Cushing's syndrome has *not* been shown to cause diabetic retinopathy more frequently than do other types of diabetes, may be partially attributable to variations in duration of diabetes: when diabetic retinopathy develops in a patient having Cushing's syndrome, the duration of the diabetes usually has been shorter than when diabetic retinopathy develops in a patient who does not have Cushing's syndrome.

It is unlikely that adrenocortical hyperfunction is a common cause of diabetes mellitus. The correction of steroid excess and/or the "cure" of Cushing's syndrome almost invariably result in the disappearance of diabetes, and those patients who have been known to have adrenal deficiency superimposed on diabetes mellitus have persistent diabetes.

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**Former Staff Member.*

***Research Fellow of the Canadian Life Insurance Officer's Association; Research Associate, The Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.*

†Research Assistant, The Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces the following Postgraduate Continuation Course on February 8 and 9, 1956

GENERAL PRACTICE

Sponsored by the Cleveland Chapter of the

American Academy of General Practice

Wednesday, February 8, 1956

Morning Session

8:00- 8:55 a.m.	.	Registration
8:55- 9:00 a.m.	.	Welcome . . . . C. L. LEEDHAM, M.D., AND H. W. SALTER, M.D.*
9:00- 9:20 a.m.	.	The Brain-Injured Child . . . . . R. D. MERCER, M.D.
9:20- 9:40 a.m.	.	Community Effort in the Treatment of Cerebral Palsy . . . . . P. A. NELSON, M.D.
9:40-10:00 a.m.	.	Neurectomy in the Treatment of Cerebral Palsy . . . . . A. W. HUMPHRIES, M.D.
10:00-10:25 a.m.	.	The Present Status of Poliomyelitis Vaccine . . . . . F. C. ROBBINS, M.D.†
10:25-10:40 a.m.	.	Questions and Answers
10:40-10:55 a.m.	.	Coffee Break
10:55-11:15 a.m.	.	Obstetrical Complications and Neonatal Death . . . . . H. P. TAYLOR, M.D.
11:15-11:35 a.m.	.	Trends in Gynecologic Therapy . . . . . J. S. KRIEGER, M.D.
11:35-11:55 a.m.	.	Papanicolaou Smears . . . . . L. J. MCCORMACK, M.D.
11:55-12:15 p.m.	.	Bleeding of Early Pregnancy . . . . . ALBERT LAMMERT, M.D.
12:15-12:30 p.m.	.	Questions and Answers
12:30 p.m.	.	Luncheon—Courtesy of Bunts Institute

Afternoon Session

1:30- 1:50 p.m.	.	New Approach to Therapy of Tic Douloureux . . . . . PALLE TAARNHØJ, M.D.
1:50- 2:10 p.m.	.	Management of Patients with Renal Lithiasis. C. C. HIGGINS, M.D.
2:10- 2:30 p.m.	.	Long-Term Care of Ileostomy . . . . R. B. TURNBULL, JR., M.D.
2:30- 2:50 p.m.	.	Common Sense in Cancer Surgery . . . GEORGE CRILE, JR., M.D.
2:50- 3:05 p.m.	.	Coffee Break
3:05- 3:25 p.m.	.	Emergency Treatment of Chest Injuries . . . D. B. EFFLER, M.D.
3:25- 3:45 p.m.	.	Emergency Treatment of Burns . . . . . ROBIN ANDERSON, M.D.
3:45- 4:05 p.m.	.	Emergency Treatment of Abdominal Injuries . . . . . GEORGE CRILE, JR., M.D.
4:05- 4:30 p.m.	.	Panel Discussion: Acute Surgical Emergencies . . . . . GEORGE CRILE, JR., M.D., Moderator ROBIN ANDERSON, M.D. D. B. EFFLER, M.D. R. B. TURNBULL, JR., M.D.

*Chairman, Education Committee, Cleveland Chapter of the American Academy of General Practice.
†Guest Speaker.* *(Affiliations on page 64)*

Thursday, February 9, 1956

Morning Session

9:00- 9:20 a.m.	Advances in Dermatological Therapy	G. H. Curtis, M.D.
9:20- 9:40 a.m.	Early Diagnosis of Collagen Disease	J. R. Haserick, M.D.
9:40-10:00 a.m.	Progress in the Management of Hypertension	Harriet Dustan, M.D.
10:00-10:20 a.m.	Advances in the Management of Uremia	W. J. Kolff, M.D.
10:20-10:30 a.m.	Questions and Answers	
10:30-10:45 a.m.	Coffee Break	
10:45-11:05 a.m.	Peripheral Vascular Disease	F. A. LeFevre, M.D.
11:05-11:25 a.m.	Movie: Aortic Graft for Arteriosclerosis Obliterans	A. W. Humphries, M.D.
11:25-11:45 a.m.	The Problem of Amebiasis	C. H. Brown, M.D.
11:45-12:05 p.m.	Primary Aldosteronism	J. S. Hewlett, M.D.
12:05-12:15 p.m.	Questions and Answers	
12:15-12:30 p.m.	Coffee Break	
12:30-12:50 p.m.	Newer Therapeutic Tools in Cardiovascular Disease	A. C. Ernstene, M.D.
12:50- 1:30 p.m.	Panel Discussion: Acute Medical Emergencies	A. C. Ernstene, M.D., Moderator E. N. Collins, M.D. F. A. LeFevre, M.D. P. G. Skillern, M.D.

Affiliations of Guest Speaker

FREDERICK C. ROBBINS, M.D., Director of Pediatrics and Contagious Disease, Cleveland City Hospital; Professor of Pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio

REGISTRATION BLANK

Educational Secretary
The Frank E. Bunts Educational Institute
Cleveland Clinic
East 93 Street and Euclid Avenue
Cleveland 6, Ohio

Please enroll me in the "General Practice Course" to be given February 8 and 9, 1956. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, February 8.

Checks should be made payable to The Frank E. Bunts Educational Institute.

Name . . . . . .

Address . . . . . .

Medical School and
Date of Graduation . . . . . .

This course is open only to graduates of approved medical schools.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

announces the following Postgraduate Course on March 14 and 15, 1956

MEDICAL PROGRESS AND ITS RELATIONSHIP TO DENTISTRY

Sponsored by the

Cleveland Dental Society

Wednesday, March 14, 1956

Morning Session

C. A. RESCH, D.D.S., Presiding

8:30- 9:15 a.m.	.	Registration
9:15- 9:20 a.m.	.	Welcome . . . . . C. L. LEEDHAM, M.D.
9:20- 9:30 a.m.	.	Opening Remarks . . . . . T. J. HILL, D.D.S.*
9:30- 9:50 a.m.	.	Otolaryngological Problems in Dentistry . WILLARD PARKER, M.D.
9:50-10:10 a.m.	.	Pediatrics in Dentistry . . . . . R. D. MERCER, M.D.
10:10-10:30 a.m.	.	Dentistry in Paraplegics . . . . . J. K. DUNN, D.D.S.
10:30-10:50 a.m.	.	Coffee Break
10:50-11:10 a.m.	.	The Dentist's Own Problem: Hypertension . . . . . HARRIET DUSTAN, M.D.
11:10-11:30 a.m.	.	The Dentist's Own Problem: Orthopedic . . G. S. PHALEN, M.D.
11:30-11:50 a.m.	.	The Dentist's Own Problem: Eye Strain . . . . . GEORGE LOCKHART, III, M.D.
11:50-12:15 p.m.	.	Questions and Answers
12:30- 1:30 p.m.	.	Luncheon—Courtesy of Bunts Institute

Afternoon Session

DWIGHT R. KINSLEY, D.D.S.,* Presiding

2:00- 2:50 p.m.	.	Skeletal Metabolism . . . . . W. D. ARMSTRONG, M.D.* Introduction by T. J. Hill, D.D.S.*
2:50- 3:20 p.m.	.	Some Clinical Effects of Parathyroid Disease . . . . . E. P. MCCULLAGH, M.D.
3:20- 3:40 p.m.	.	Blood Dyscrasias . . . . . J. D. BATTLE, JR., M.D.
3:40- 4:00 p.m.	.	Coffee Break
4:00- 4:30 p.m.	.	The Year in Dental Research . . . . . T. J. HILL, D.D.S.*
4:30- 4:45 p.m.	.	Questions and Answers

*Guest Speaker. (*Affiliations on page 66*)

Thursday, March 15, 1956

Morning Session

J. K. Dunn, D.D.S., Presiding

9:30- 9:50 a.m.	Stress	A. C. Corcoran, M.D.
9:50-10:10 a.m.	Headache	L. L. Lovshin, M.D.
10:10-10:30 a.m.	Neuralgias	A. T. Bunts, M.D.
10:30-10:45 a.m.	Tic Douloureux	Palle Taarnhøj, M.D.
10:45-11:05 a.m.	Coffee Break	
11:05-11:25 a.m.	Dermatological Lesions of the Face	E. W. Netherton, M.D.
11:25-11:45 a.m.	Collagen Disease	J. R. Haserick, M.D.
11:45-12:30 p.m.	Panel Discussion: Advances in Medicine and Dentistry	T. J. Hill, D.D.S.,* Moderator W. D. Armstrong, M.D.* A. C. Ernstene, M.D. A. H. Kniesner, D.D.S.* E. P. McCullagh, M.D.

Affiliations of Guest Speakers

WALLACE D. ARMSTRONG, M.D., Head of the Department of Physiological Chemistry, University of Minnesota Medical School, Minneapolis, Minnesota.
THOMAS J. HILL, D.D.S., Professor Emeritus of Oral Pathology, Western Reserve University School of Dentistry, Cleveland, Ohio.
DWIGHT R. KINSLEY, D.D.S., President, Cleveland Dental Society, Cleveland, Ohio.
ALBERT H. KNIESNER, D.D.S., Assistant Professor of Pathology and Peridontia, Western Reserve University School of Dentistry, Cleveland, Ohio.

**Guest Speaker*

REGISTRATION BLANK

Educational Secretary
The Frank E. Bunts Educational Institute
Cleveland Clinic
East 93 Street and Euclid Avenue
Cleveland 6, Ohio

Please enroll me in the course on "Medical Progress and Its Relationship to Dentistry" to be given March 14 and 15, 1956. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, March 14.

Checks should be made payable to The Frank E. Bunts Educational Institute.

Name . . . . . .

Address . . . . . .

Medical or Dental School and
Date of Graduation . . . . . .

This course is open only to graduates of approved medical or dental schools.